# STATISTICAL ANALYSIS PLAN

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|---|---|
| **Protocol title:** | **A Phase 2B, randomized, double-blind, placebo-controlled, 2-stage seamless study to evaluate the efficacy, safety, pharmacodynamics, and pharmacokinetics of lademirsen (SAR339375) for once weekly subcutaneous injection in patients aged 12 years and older with Alport Syndrome** |
| **Protocol number:** | **Amended Protocol 13** |
| **Compound number (INN/Trademark):** | **SAR339375**<br>**(lademirsen/Not applicable)** |
| **Study phase:** | **Phase 2B** |
| **Short title:** | **HERA** |
| **Statistician:** | [redacted] |
| **Statistical project leader:** | [redacted] |
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# VERSION HISTORY

**Table 1 - Major changes in statistical analysis plan**

| SAP Version | Approval Date | Changes | Rationale |
|---|---|---|---|
| 1.0 | 15-Apr-2022<br>(Prior to the 1st DBL) | Not Applicable | Original version |
| 2.0 | 04-May-2022 | • Updated the age range in the study title in cover page to align with protocol amendment 13<br>• Corrected "Unconditional - Binding futility" for type 1 error from 0.8% to 1.4%, and for overall power from 70.8% to 74.5% in Table 4<br>• Updated "the Handling of potentially clinically significant abnormalities" when the PCSA criteria is composite in Section 5.3<br>• Corrected typos in the SAS code in Section 5.6<br>• Clarified that conjugated bilirubin is the same as direct bilirubin in Section 5.8<br>• Added the PCSA criteria for Glucose in Section 5.8 | Clarifications and correlations |

# 1 INTRODUCTION

## 1.1 STUDY DESIGN

This will be a randomized, double-blind, placebo-controlled, multi-center, Phase 2B study conducted in approximately 130 subjects (including 43 subjects in Stage 1/Cohort 1 and approximately 87 subjects in Stage 2/Cohort 2) with Alport Syndrome.

This study will have two stages:

- Stage 1/Cohort 1 (patients in the ongoing Phase 2 study, randomization completed by the end of December 2021) includes 48-week double-blind, placebo-controlled period followed by 96 weeks open label treatment period with lademirsen and 10 weeks post-treatment follow up period.
- Stage 2/Cohort 2 includes 96-week double-blind, placebo-controlled period followed by 48 weeks open label treatment period with lademirsen and 10 weeks post-treatment follow up period.

For Stage 1, 43 eligible subjects are randomized in a 2:1 ratio to receive every week (QW) subcutaneous (SC) doses of lademirsen 110 mg or placebo for 48 weeks with stratification by screening eGFR (<60 mL/min/1.73 $m^2$ versus ≥60 mL/min/1.73 $m^2$). At the completion of 48 weeks of double-blind, placebo-controlled treatment, all subjects will be eligible to roll over into a 96 week open-label treatment extension period in which all subjects will receive QW active treatment with lademirsen.

Two interim analyses will be conducted using data from Stage 1:

[redacted]

For Stage 2, an additional 87 eligible subjects will be randomized in a 2:1 ratio to receive every week subcutaneous doses of lademirsen, either110 mg (adults) or 1.5 mg/kg (adolescents), or placebo for 96 weeks. Stratification by screening eGFR level (≤35 mL/min/1.73 $m^2$, versus >35 to <60 mL/min/1.73 $m^2$, versus ≥60 mL/min/1.73 $m^2$), age category (<18 years old versus ≥18 years old, and screening SGLT2 inhibitor treatment (with versus without SGLT2 inhibitor treatment) will be performed. At the completion of 96 weeks of double-blind, placebo-controlled treatment, all subjects will be eligible to roll over into a 48-week open-label treatment extension period in which all subjects will receive QW active treatment with lademirsen.

Among 87 Stage 2 subjects, 12 subjects with screening eGFR 20 to 35 mL/min/1.73 $m^2$ will be included due to regulatory request to assess the safety of lademirsen in subjects with low baseline eGFR values. Therefore, those 12 subjects will not be included into the primary and secondary efficacy analyses; thus only subjects from Stage 2 with screening eGFR >35 mL/min/1.73 $m^2$ will be included in these efficacy analyses (75 Stage 2 subjects).

[redacted]

Otherwise, all Stage 2 subjects will continue their randomized double blind treatment period until the completion of 96 weeks period before rolling over into a 48 week open label extension study, and a final efficacy analysis will be conducted when all Stage 2 subjects complete 96 weeks double blind treatment period.

## 1.2 OBJECTIVE AND ENDPOINTS

**Table 2 - Objectives and endpoints**

| Population | Objectives | Endpoints |
|---|---|---|
| **Primary** | | |
| Primary population[a] | To assess the efficacy of lademirsen in reducing the rate of decline in kidney function as compared to placebo in participants at risk for rapidly progressive Alport syndrome | Annualized rate of change in estimated glomerular filtration rate (eGFR) during the placebo-controlled treatment period |
| **Secondary** | | |
| Primary population[a] | To assess the efficacy of lademirsen in reducing the absolute decline in kidney function at Week 48 (using both Stage 1 and Stage 2 data) and Week 96 (using Stage 2 data only) | Absolute change in eGFR values from baseline at Week 48 (using both Stage 1 and Stage 2 data), and Week 96 (using Stage 2 data only) of placebo-controlled treatment period |
| Primary population[a] | To assess the efficacy of lademirsen in delaying time to reach the composite endpoint, that includes ≥40% reduction in eGFR, kidney failure (defined by an eGFR ≤15 mL/min/1.73 $m^2$ at two consecutive visits, or initiation of hemodialysis or kidney transplant) | Time to reach the composite endpoint that included ≥40% reduction in eGFR, kidney failure (defined by an eGFR ≤15 mL/min/1.73 $m^2$ at two consecutive visits or initiation of hemodialysis or kidney transplantation) during placebo-controlled treatment period |

| Population | Objectives | Endpoints |
|---|---|---|
| Stage 2 Primary population[a] | To assess the efficacy of lademirsen in Fatigue at Week 48 | Percentage change from baseline in fatigue, as measured by the FACIT-F scales, at Week 48 during the Stage 2 placebo-controlled treatment period, in the primary population<br><br>Percent of participants experiencing a meaningful worsening in their fatigue, measured by the FACIT-F scales, at Week 48 during the Stage 2 placebo-controlled treatment period, in the primary population |
| Safety population[c] | To assess the safety and tolerability of lademirsen in subjects with Alport syndrome. | Incidence and severity of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)<br>Observed values and changes from baseline in clinical laboratory parameters (eg, hematology, chemistry, complement, and urinalysis)<br>Observed values and changes from baseline in vital signs<br>Observed changes from baseline in 12-lead electrocardiogram (ECG)<br>Observed changes from baseline in physical examinations<br>Growth and development (including tanner staging) for adolescent participants (12 to <18 years inclusive) (Stage 2 only). |
| PK population[d] | To assess plasma pharmacokinetic (PK) parameters. Concentration at 4 hours post dosing (approximate Cmax for the parent compound) for lademirsen, its active major metabolite (RG0005), and the sum of lademirsen and RG0005 (SUM) following administration of lademirsen. Ctrough will be assessed in terms of SUM only. | Plasma concentrations of lademirsen, RG0005, and SUM (lademirsen + RG0005) in Cmax samples and SUM only in Ctrough samples. |
| ADA population[e] | To assess potential formation of anti-drug antibodies (ADAs) following administration of lademirsen. | Incidence and titer of ADAs<br>Association of ADAs with adverse events incidence |
| Primary population[a] | To assess the pharmacodynamic effect of lademirsen on miR-21 and on changes in kidney injury and function biomarkers. | • Changes in circulating miR-21 at Week 24, Week 48 (using both Stage 1 and Stage 2 data), and Week 96 (using Stage 2 data only) during the placebo-controlled treatment period in the primary population.<br>• Change in kidney injury and function biomarkers from baseline at Weeks 24 and 48 (using both Stage 1 and Stage 2 data) and Week 96 (using Stage 2 data only) during the placebo-controlled treatment period in the primary population:<br>- In blood: blood urea nitrogen (BUN);<br>- In urine: protein/creatinine ratio, albumin/creatinine ratio, and epidermal growth factor (EGF);<br>• In both blood and urine: creatinine, Cystatin C, transforming growth factor-β (TGFβ), and neutrophil gelatinase-associated lipocalin (NGAL). |

| Population | Objectives | Endpoints |
|---|---|---|
| **Exploratory** | | |
| Secondary population[b] | To assess the efficacy of lademirsen in reducing the decline in kidney function at Week 48 (using both Stage 1 and Stage 2 data) and Week 96 (using Stage 2 data only). | Absolute change in eGFR values from baseline at Week 48 (using both Stage 1 and Stage 2 data), and Week 96 (using Stage 2 data only) during the placebo-controlled treatment period |
| Secondary population[b] | To assess the efficacy of lademirsen in delaying time to composite endpoint | Time to reach the composite endpoint that included ≥40% reduction in eGFR, kidney failure (defined by an eGFR ≤15 mL/min/1.73 $m^2$ at two consecutive visits or initiation of hemodialysis or kidney transplantation) during placebo-controlled treatment period |
| Primary population[a] | To assess the effect of lademirsen on urine and blood biomarkers in Alport Syndrome subjects. | Changes in exploratory biomarkers from baseline at Weeks 24 and 48 (using both Stage 1 and Stage 2 data) and Week 96 (using Stage 2 data only), which may include but are not necessarily limited to:<br>• In blood only: microRNAs (miRs) other than miR-21<br>• In both blood and urine: β-2 microglobulin and connective tissue growth factor (CTGF)<br>• In urine only: kidney injury molecule-1 (KIM-1) and calbindin-D28k |
| Stage 2 Primary population[a] | To assess the efficacy of lademirsen in Fatigue at Week 96 | Percentage change from baseline in fatigue, as measured by the FACIT-F scales, at Week 96 during the Stage 2 placebo-controlled treatment period<br>The percentage of participants experiencing meaningful worsening in their fatigue, as measured by the FACIT-F scales at week 96 during the Stage 2 placebo-controlled treatment period. |
| Stage 2 Primary population[a] | To assess the efficacy of lademirsen in health-related quality of life | Change from baseline in health-related quality of life as measured by KDQOL-36 for adult participants at Weeks 48 and 96 during the Stage 2 placebo-controlled treatment period<br>Change from baseline in health-related quality of life as measured by Pediatric Quality of Life Inventory (PedsQL) general core scales for patients aged 12 to <18 years at Weeks 48 and 96 during the Stage 2 placebo-controlled treatment period. |
| Stage 2 Primary population[a] | To assess the effect of lademirsen on patients' global impression of severity (PGIS) of symptoms | Change from baseline in PGIS at Weeks 48 and 96 during the Stage 2 placebo-controlled treatment period |
| Stage 2 Primary population[a] | To assess the effect of lademirsen on patients' global impression of change (PGIC) of symptoms in Stage 2 primary population | Summary of PGIC at Weeks 48 and 96 during the Stage 2 placebo-controlled treatment period |
| Primary population | To assess the efficacy of lademirsen in reducing the decline in hearing sensitivities at Week 48 and Week 96.<br>Please see Protocol Section 10.5.2 for China-specific exploratory objectives. | Change from baseline at Week 48 and Week 96 in degrees of hearing level recorded in both ears measured by a pure tone audiometry (using both Stage 1 and Stage 2 data of the placebo controlled treatment period) |

*a* Primary population excludes subjects who had baseline eGFR of 20 to 35 mL/min/1.73 $m^2$; Stage 2 Primary population are primary population from Stage 2 only.
*b* Secondary population include all randomized subjects; Stage 2 Secondary population are secondary population from Stage 2 only.
*c* Safety population include all randomized subjects who take at least 1 dose of study intervention.
*d* PK population include all treated participants (safety population) who receive at least one dose of lademirsen with at least one post-baseline PK sample for determination of lademirsen concentrations.
*e* ADA population include all randomized and treated participants (safety population) who had at least one post-baseline ADA sample.

### 1.2.1 Estimands

Primary estimand defined for main endpoints are summarized in below Table 3. More details are provided in Section 4.

For all estimands on the placebo-controlled treatment period, the comparison of interest will be the comparison of lademirsen versus placebo.

**Table 3 - Summary of primary estimand for main endpoints**

| Endpoint Category (estimand) | Estimands | | | |
|---|---|---|---|---|
| | **Endpoint** | **Population** | **Intercurrent event(s) handling strategy** | **Population-level summary (Analysis and missing data handling)** |
| **Primary objective:** To assess the efficacy of lademirsen in reducing the rate of decline in kidney function as compared to placebo in subjects at risk for rapidly progressive Alport syndrome | | | | |
| Primary endpoint (treatment policy estimand) | Annualized rate of change in estimated glomerular filtration rate (eGFR) during placebo-controlled treatment period | Primary population | Regardless of whether or not subjects completed the placebo-controlled treatment period. Those data collected after the study drug discontinuation during follow up period that is within 48 weeks for Stage 1 subjects or with 96 weeks for Stage 2 subjects since first IMP during the placebo-controlled treatment period will be included. However, data collected after kidney transplantation or hemodialysis will not be included. | Annualized rate of change in eGFR during the placebo-controlled treatment period will be compared between lademirsen and placebo using a linear mixed effect model. The model will include random intercept and random slope for time to account for the between subject variability. Time will be treated as a continuous variable based on actual eGFR assessment date relative to the randomization date.<br>All the data up to Week 96 during the placebo-controlled treatment period will be included in the analysis regardless of missing data that no missing data imputation will be conducted. |

# 2 SAMPLE SIZE DETERMINATION

This study has two stages as described in Section 1.1. It also has three interim analyses planned as described in Section 4.9.

[redacted]

With total sample size of 118 (43+75) subjects for the primary efficacy analyses, the study will provide approximately 92.6% (regardless of two interim futility analyses decision) power at either formal interim analysis for efficacy (3rd interim analysis) or final analysis to detect a reduced rate of decline of 5 mL/min/1.73 $m^2$/year (~50% reduction) in eGFR annualized rate under lademirsen treatment, in comparison to placebo.

The power calculations were based on simulations of a frequentist random coefficient linear mixed effect model which is detailed in Section 4.3.2. For the simulation, the following model parameters were obtained from analysis of the ATHENA Natural History Study (OBS16374) data:

- Average linear decline in eGFR of 10 mL/min/1.73 $m^2$/year in placebo arm
- Standard deviation (SD) for the residual error of eGFR of [redacted] mL/min/1.73 $m^2$ and SD for random effect of slope to be [redacted] mL/min/1.73 $m^2$/year
- Uniform enrollment of 1 years for 43 subjects from Stage 1, and uniform enrollment of additional 1.67 years for additional 75 subjects from Stage 2. Also at the time of interim efficacy analyses (3rd interim analysis), all 43 subjects at Stage 1 already completed the 48 weeks double blind treatment period.
- In addition, 10% annual dropout rate overall for both Stage 1 and Stage 2 subjects with exponential distribution for time to dropout was assumed.

[redacted]

# 3 RESPECTIVELY ANALYSIS POPULATIONS

The following populations for analyses are defined:

**Table 5 - Populations for analyses**

| Population | Description |
|---|---|
| Primary population | All randomized participants from Stage 1/Cohort 1 and Stage 2/Cohort 2 excluding subjects with low baseline eGFR (ie, baseline eGFR of 20 to 35 mL/min/1.73 $m^2$).<br>Participants will be analyzed according to the intervention allocated by randomization. |
| Stage 2 Primary population | Primary population in Stage 2/Cohort 2 only. |
| Secondary population | All randomized participants from Stage 1/Cohort 1 and Stage 2/Cohort 2 including subjects with low baseline eGFR (ie, baseline eGFR of 20 to 35 mL/min/1.73 $m^2$).<br>Participants will be analyzed according to the intervention allocated by randomization. |
| Stage 2 Secondary population | Secondary population in Stage 2/Cohort 2 only. |
| Safety population | All randomized participants from Stage 1/Cohort 1 and Stage 2/Cohort 2 who took at least 1 dose of study intervention. Participants will be analyzed according to the study intervention they actually received. |
| PK population | All treated participants from Stage 1/Cohort 1 and Stage 2/Cohort 2 who received at least one dose of the lademirsen and had at least one post does PK sample for determination of lademirsen concentrations. |
| ADA population | All randomized and treated participants (safety population) who had at least one post-baseline ADA sample from Stage 1/Cohort 1 and Stage 2/Cohort 2. |
| Lademirsen treated population | Randomized population who actually received at least 1 or partial dose of lademirsen during the study |

# 4 STATISTICAL ANALYSES

## 4.1 GENERAL CONSIDERATIONS

For the analyses for the primary, secondary and tertiary/exploratory objectives, the corresponding analyses population are summarized in Table 2 and Table 5, and the analyses period is on the double blind placebo-controlled period.

However, the analyses for placebo controlled and open label treatment period combined are discussed in Section 4.8.5.

***Observation period***

The observation period will be divided into the following segments:

The **pre-treatment period** is defined as the time from the signed informed consent (and ascent for adolescent in Stage 2) date up to the first administration of the IMP.

For the **placebo-controlled treatment period**, the treatment-emergent (TE) period is defined as the period from the first IMP administration to

- the first administration of the IMP in open-label extension period for participants who entered open-label extension period or,
- the last administration of the IMP + 7 days if the participant is ongoing or not continuing in open-label treatment extension period (eg, early discontinuation of treatment).

For the **lademirsen treatment period**, the TE period is defined as the period from the first lademirsen administration the last administration of lademirsen + 7 days. The period is defined for participants who had at least 1 full or partial administration of lademirsen.

For the **overall study period**, the TE period is defined as from the first IMP administration to the last administration of the IMP + 7 days.

For the **post-treatment period**, it is defined as the period from the end of overall study TE period until the end of the study (eg, the later day of the last scheduled visit, or the end-of-study date collected on e-CRF page “Completion of End of Study/Follow-up”. If death is the end-of-study reason, date of death will be used.)

The TE period and on-treatment period are defined the same, therefore, the wording may be used interchangeably.

The lademirsen treatment period and overall study period are used for analysis in Section 4.8.5.

In general, for analysis in the **placebo-controlled treatment period**, the baseline is the last available value prior to first IMP. For analysis in the **lademirsen treatment period**, the baseline is the last available value prior to the first administration of lademirsen.

## 4.2 PARTICIPANT DISPOSITION

For participant study status, the total number of participants in each of the following categories will be presented using a summary table:

- Nonrandomized but treated participants
- Randomized participants
- Randomized but not treated participants
- Randomized and treated participants
  - Participants who completed the double-blinded, placebo-controlled study treatment period as per protocol
  - Participants who are ongoing the double-blinded, placebo-controlled study treatment period as per protocol
  - Participants who did not complete (eg, treatment early discontinuation) the double-blinded, placebo-controlled study treatment period as per protocol
    - Reasons for treatment discontinuation during the double-blinded, placebo-controlled study treatment period
    - Specified reason for treatment withdrawal by participant during the double-blinded, placebo-controlled study treatment period
  - Participants who completed the open-label extension study treatment period as per protocol
  - Participants who are ongoing the open-label extension study treatment period as per protocol
  - Participants who did not complete (eg, early treatment discontinuation) the open-label extension study treatment period as per protocol
    - Reasons for treatment discontinuation during the open-label extension study treatment period
    - Specified reason with treatment withdrawal by participant during the open-label extension study treatment period
  - Participants who completed the study
  - Participants who withdraw from study
  - Participants who withdraw from study by main reason of study discontinuation
  - Status at last study contact

For all categories of participants (except for nonrandomized categories) percentage will be calculated using the number of randomized participants as the denominator. Reasons for treatment discontinuation will be also provided.

## 4.3 PRIMARY ENDPOINT(S) ANALYSIS

### 4.3.1 Definition of endpoint(s)

Primary endpoint is annualized rate of change in eGFR during the placebo-controlled treatment period.

For subjects with age greater than 16 years informed consent or assent for adolescent, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine Equation 2021 (1) will be used for calculating eGFR.

For subjects with age 12-16 (both inclusive) informed consent or assent for adolescent, the Schwartz equation (2) will be used.

**CKD-EPI Creatinine equation (2021)** (1)

$eGFR = 142 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.200} \times 0.9938^{Age} \times 1.012$ [if female], where Scr is serum creatinine in mg/dL, $\kappa$ is 0.7 for females and 0.9 for males, $\alpha$ is -0.241 for females and -0.302 for males. And unit of age is years, which should be calculated to reflect the age at the time when creatinine is measured. The age = (lab sampling date - inform consent date)/365.25 + Age at inform consent.

**Schwartz equation (2009)** (2)

eGFR = 0.413 x (height/Scr) if body-height is expressed in centimeters OR 41.3 x (height/Scr) if body-height is expressed in meters, where Scr is standardized creatinine in mg/dL.

### 4.3.2 Main analytical approach

Annualized rate of change in eGFR (slope of eGFR) during the placebo-controlled treatment period will be compared between lademirsen and placebo using a random coefficient linear mixed effect model which includes time as a continuous variable for Stage 1 and Stage 2 subjects combined.

The model will include eGFR measurements from baseline to end of double blind, placebo-controlled period (48 weeks for Stage 1 subjects, up to 96 weeks for Stage 2 subjects) as response variables, and it will include fix effects of treatment (lademirsen or placebo), screening eGFR stratification factor ($\leq$35 mL/min/1.73 $m^2$ , versus >35 to <60 mL/min/1.73 $m^2$ , versus $\geq$60 mL/min/1.73 $m^2$), age category (<18 versus $\geq$18 years old), SGLT2 inhibitor treatment (with versus without), time, and treatment-by-time interaction. In addition, it will include random intercept and random slope for time to account for the between subject variability. Time will be treated as a continuous variable based on actual eGFR assessment date relative to the randomization date as defined in Section 5.2 (Derivation of "year" for eGFR slope analysis). An unstructured variance-covariance matrix shared across treatment groups will be used to model the variance-covariance matrix for random intercept and random slope using RANDOM statement in PROC MIXED. The model will be fitted using restricted maximum likelihood. Residual errors are assumed to be independent, normally distributed, with a homogeneous variance.

Difference in estimated least square mean slope of eGFR, corresponding 95% CI, and p-value will be presented.

The primary estimand will be the difference in mean slope of eGFR estimated from baseline to up to 96 weeks during the double-blind treatment period in primary population, regardless of whether or not subjects completed the study period of 48 weeks for Stage 1 subjects or the study period of 96 weeks for Stage 2 subjects (eg, early treatment discontinuation). Those data collected after the study drug discontinuation during the follow up period that is within 48 weeks for Stage 1 subjects or with 96 weeks for Stage 2 subjects since first IMP will be included. However, data collected after kidney transplantation or start of hemodialysis will not be included.

The sample SAS programming code for the analysis model is provided in SAS macro for MMRM part of Section 5.6 and also provided below with stratification factors considered.

[redacted]

### 4.3.3 Sensitivity analyses

#### *4.3.3.1 Sensitivity analysis to assess the robustness of the variability assumption*

To assess the robustness of the variability assumption, annualized rate of change in eGFR (slope of eGFR) during the placebo-controlled treatment period will also be analyzed with the same random coefficient linear mixed effect model as specified in Section 4.3.2, with the exception that R side variance covariance matrix for within subject errors will also be applied (using REPEATED statement in SAS PROC MIXED).

R side variance covariance matrix will first be fitted with unstructured (UN), and if the model does not converge with both Hessian and the G matrix being positive definite, the model will be fit using the covariance matrices of the following order specified by a decreasing number of covariance parameters until convergency is met:

- Heterogeneous Toeplitz (TOEPH)
- Heterogeneous First-order autoregressive (ARH(1))
- Toeplitz (TOEP)
- First-order autoregressive (AR(1))
- Heterogeneous compound symmetry (CSH)
- Compound symmetry (CS)

The first covariance structure yielding convergence will be used in the analysis. When the unstructured covariance matrix is used, the Kenward-Roger approximation (DDFM=KR in SAS PROC MIXED) will be used to estimate the denominator degrees of freedom, otherwise, denominator degrees of freedom will be estimated using the between within method (DDFM=BW in SAS PROC MIXED).

#### *4.3.3.2 Sensitivity analysis to assess the robustness of lademirsen treatment effect using only first year data*

To assess the robustness of lademirsen treatment effect using first year data, annualized rate of change in eGFR (slope of eGFR) during the placebo-controlled treatment period will also be analyzed with the same random coefficient linear mixed effect model as specified in Section 4.3.2, but excluding any data collected beyond Week 48 for Stage 2 subjects.

#### *4.3.3.3 Sensitivity analysis using two step linear regression approach*

In the two-step linear regression approach to estimate mean eGFR slope, first, each participant's eGFR slope will be estimated separately by regressing the participant's repeated eGFR value on the time variable as defined in Section 5.2 (Derivation of "year" for eGFR slope analysis). Second, the eGFR slopes for all participants calculated in the first step will be treated as the outcome variable and fitted into a different linear regression model.

Specifically, **for the first step**, for each subject from both Stage 1 and 2, a linear regression model will be applied with longitudinal post-baseline eGFR during placebo-control treatment period (48 weeks for Stage 1 subjects, up to 96 weeks for Stage 2 subjects) as dependent variable, and longitudinal visit for each eGFR measurement in unit of year as covariate to estimate the individual participant's eGFR slope at placebo-controlled treatment period.

**For the second step**, the mean eGFR slope will be estimated in another weighted linear regression model by taking the individual participant's eGFR slope at placebo-controlled treatment period estimated from first step from all subjects from both Stage 1 and 2 as the dependent variable. The model will include covariate of treatment group (lademirsen or placebo), screening eGFR stratification factor, age categories (<18 versus >=18 years old), and SGLT2 inhibitor treatment at time of screening (versus those without SGLT2 treatment at screening). For each subject, the weight will be the sum of the square of difference in each subject's time to the mean time of the same subject, ie, weight for subject *i* is as follows:

$w_i = \sum_{j=1}^{n_i}(t_{ij} - \bar{t}_i)^2$ , where $t_{ij}$ is the time *j* for subject *i* and $\bar{t}_i$ is the mean time for subject, and $n_i$ is the number of time points for subject *i*.

The summary statistics for mean eGFR slopes estimated at placebo-controlled treatment period, including the estimated LS means and SEs, corresponding 95% CIs, and p-values will be presented by treatment group and difference between treatment groups.

Separately, the summary statistics for eGFR slope during screening period will also be calculated with the similar approach with the exception that screening eGFR stratification factor, age categories (<18 versus >=18 years old), SGLT2 inhibitor treatment at time of screening (versus those without SGLT2 treatment at screening). will not be included as in the model **at second step**.

For visualization purpose, the individual participant's slope at screening period and the placebo-controlled treatment period will be displayed side by side in spaghetti plots by treatment group.

### 4.3.4 Supplementary analysis (while on treatment estimand)

In this analysis, the same method as in Section 4.3.2 will be used to estimate the difference in mean slope of eGFR estimated during the placebo-control treatment period. However, efficacy assessments obtained after IMP discontinuation or introduction of rescue therapy will not be included. This analysis is corresponding to "while on treatment estimand".

## 4.4 SECONDARY ENDPOINT(S) ANALYSIS

This section will describe the key secondary efficacy endpoints that will be used for the multiplicity adjustment.

### 4.4.1 Key/confirmatory secondary endpoint(s)

#### *4.4.1.1 Definition of endpoint(s)*

- Absolute change in eGFR values from baseline at Week 48 (using both Stage 1 and Stage 2 data), and Week 96 (using Stage 2 data only) during the placebo-controlled treatment period
- Time to reach the composite endpoint that includes ≥40% reduction in eGFR, or kidney failure (defined by an eGFR ≤15 mL/min/1.73 $m^2$ at two consecutive visits or initiation of hemodialysis, or kidney transplant) during the placebo-controlled treatment period
- Percentage change from baseline in fatigue, as measured by the FACIT-F scales at Week 48 during the Stage 2 placebo-controlled treatment period, in the primary population
- Percentage of participants experiencing meaningful worsening in their fatigue, measured by the FACIT-F scales, at Week 48 during the Stage 2 placebo-controlled period, in the primary population.

The FACIT-F is a 40-item measure that assesses self-reported fatigue and its impact on daily activities and functions. The FACIT-Fatigue subscale will be used to measure fatigue in adult participants from Stage 2 of the study. The FACIT-F was designed to measure fatigue associated with anemia among cancer patients, but has been used widely across numerous therapeutic areas, including patients with kidney disease (4, 5). The FACIT-F includes 13 items that measure the severity of fatigue [redacted] and the impact of fatigue on functioning [redacted]. Patients rate their experiences over the "past 7 days" using a 0-4 verbal rating scale ("Not at all" to "Very Much"). The complete FACIT-F Fatigue subscale is included in Figure 1. The FACIT-F is scored as a sum of all 13 of the item responses; the scale range is from 0-52. After appropriate reverse scoring of 11 items, lower scores on the FACIT-F indicate greater levels of fatigue.

A pediatric version of the FACIT-F will be administered to patients 12-17 years old (6). The Pediatric FACIT-F includes 13 items that measure the amount of time that fatigue was experienced and impacted functioning. The Pediatric FACIT-F was developed for use with pediatric cancer patients but has also been used in other areas (7). Patients rate their experiences over the "past 7 days" using a 0-4 verbal rating scale ("None of the time" to "All of the time"). The Pediatric FACIT-F scale is included in Figure 2. As consistent with the adult version, the total score scale range is from 0-52.

#### *4.4.1.2 Main analytical approach*

Similar to the primary endpoint analysis, to control the overall Type 1 error rate at one sided 0.025, the secondary endpoints will also be analyzed for double blind placebo-controlled period of Stage 1 and Stage 2 data combined.

##### *4.4.1.2.1 Analysis for absolute change in eGFR values from baseline at Weeks 48*

Combined data from both Stage 1 and Stage 2 data during placebo-controlled period will be analyzed with a mixed effects model with repeated measures (MMRM) by treating time as a categorical variable. The model will include eGFR measurements from baseline to 48 weeks of double blind, placebo-controlled period as response variables, and it will include fix effects of treatment (lademirsen or placebo), screening eGFR stratification factor, age category (<18 versus ≥18 years old), screening SGLT inhibitor treatment (with versus without), time, and treatment-by-time interaction. Time will be treated as categorical variable. Due to the potential lack of convergency due to large number of visits, only data from Week 12, 24, 36, 40, 44 and 48 will be included in the model.

To model the within patient errors, an unstructured (UN) covariance structure will first be fitted, and if the model does not converge with both Hessian and the G matrix being positive definite, the model will be re-fitted using the covariance matrices of the following order specified by a decreasing number of covariance parameters until convergency is met:

- Heterogeneous Toeplitz (TOEPH)
- Heterogeneous First-order autoregressive (AR(1))
- Homogeneous Toeplitz (TOEP)
- AR(1)
- Heterogeneous compound symmetry (CSH)
- CS

The first covariance structure yielding convergence will be used in the analysis. When the unstructured covariance matrix is used, the Kenward -Roger approximation (DDFM=KR in SAS PROC MIXED) will be used to estimate the denominator degrees of freedom, otherwise, denominator degrees of freedom will be estimated using the between within method (DDFM=BW in SAS PROC MIXED).

##### *4.4.1.2.2 Analysis for absolute change in eGFR values from baseline at Weeks 96*

Since only Stage 2 has 96 weeks placebo-controlled treatment period, for the endpoint of absolute change in eGFR values from baseline at Week 96, only Stage 2 data during placebo-controlled period will be analyzed with a mixed effects model with repeated measures (MMRM) by treating time as a categorical variable. The model will include eGFR measurements from baseline to 96 weeks of the double blind, placebo-controlled period as response variables, and it will include fix effects of treatment (lademirsen or placebo), screening eGFR stratification factor, age

category (<18 versus ≥18 years old), screening SGLT2 inhibitor treatment (versus those without), time, and treatment-by-time interaction. Time will be treated as categorical variable. The same variance-covariance matrix as specified in Section 4.4.1.2.1 will be used. Due to the potential lack of convergency due to large number of visits, only data from Week 12, 24, 36, 48, 60, 72, 84, 88, 92, 96 will be included in the model.

#### *4.4.1.2.3 Analysis for time to reach Composite endpoint during the placebo-controlled treatment period*

Time to reach composite endpoint (as defined in Section 4.4.1.1) will be summarized by treatment group using Kaplan-Meier estimate. A stratified log rank test adjusting for screening eGFR stratification factor, SGLT2 inhibitor treatment at time of screening (with versus without), and age groups (<18 versus ≥18 years old) will be used to compare between treatment groups for data from placebo-controlled period of Stages 1 and 2 combined. Subjects who have not reach composite endpoint will be censored at the last available day in double-blind period for subjects who entered into open label treatment and will be censored at the last available day in the study for subjects who discontinued study and did not enter open label treatment.

#### *4.4.1.2.4 Analysis for the patient reported outcomes*

For the percentage change in fatigue, as measured by Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scales at Week 48 of placebo-controlled period, we will only have data from Stage 2. Therefore, Stage 2 data during placebo-controlled period will be analyzed with a mixed effects model with repeated measures (MMRM) by treating time as a categorical variable. The model will include all the data from placebo-controlled period up to Week 48 as response variables, and it will include fix effects of treatment (lademirsen or placebo), baseline value, screening eGFR stratification factor, age category (<18 versus ≥18 years old), SGLT2 inhibitor treatment at screening (with versus those without), time, and treatment-by-time interaction. Time will be treated with categorical variable. The same variance-covariance matrix as specified in Section 4.4.1.2.1 will be used.

Thresholds for meaningful within-patient improvement on the FACIT-F total score at Week 48 will be calculated using blinded data from the current study with methods described in PRO Psychometric Statistical Analysis Plan. The thresholds will be added to the SAP prior to the unblinding for the interim efficacy analyses (interim analysis 3).

For FACIT-F total score, a binary endpoint will also be derived. Subjects will be defined as meeting meaningful worsening criteria at week 48 if meet or exceed the meaningful change threshold at respective weeks. For patients who have missing data at Week 48, as a conservative approach, they will be considered as meeting meaningful worsening criteria for the specific week. The binary measure of meeting meaningful worsening criteria (yes vs no) at Week 48 will be analyzed with logistic regression including treatment, screening eGFR stratification factor, age category (<18 versus ≥18 years old), screening SGLT2 inhibitor treatment (with versus without) as covariates. Number and % of responder, as well as odds ratio, 95% CI and p-value from the logistic regression model will be provided.

Cumulative distribution functions (CDFs) will be generated by treatment group for FACIT-F. The CDFs will show the cumulative percent of patients on the y-axis and percentage change from baseline to Week 48 on FACIT-F on the x-axis. The CDFs will allow a visual inspection of the cumulative proportion of patients in each treatment group who achieved various levels of percentage change on the FACIT-F at Week 48.

#### 4.4.2 Sensitivity analysis for FACIT-F

Two sensitivity analyses to ensure that the treatment effect is similar across the adult and adolescent samples for FACIT-F were proposed.

- For the first sensitivity analysis: percentage change from baseline in FACIT-F at Week 48 will be analyzed separately for adult and pediatric.
- For the second sensitivity analysis: for percentage change from baseline in FACIT-F at Week 48, only items in the adult and pediatric measures that use common language [eg, "I feel tired," "I feel weak (all over)"] will be used in calculating the total fatigue score. This will eliminate items that differentiate the 2 measures and, therefore yield a score that it based on a common assessment across the age groups.

#### 4.4.3 Supportive secondary endpoint(s)

For the supportive secondary endpoints that are safety, the main analytical approaches are discussed in Section 4.7. For the supportive secondary endpoints that are pharmacokinetic (PK), the main analytical approaches are discussed in Section 4.8.1. For the supportive secondary endpoints that are immunogenicity, the main analytical approaches are discussed in Section 4.8.2. For the supportive secondary endpoints that are biomarkers, the main analytical approaches are described in Section 4.8.4.

### 4.5 EXPLORATORY ENDPOINT(S) ANALYSIS

#### 4.5.1 Definition of endpoint(s)

The definition of exploratory endpoints are summarized in Table 2 with details provided below

- The kidney disease quality of life instrument - 36 items (KDQOL-36) is a patient-reported disease-specific measure of health-related quality of life. The KDQOL-36 includes the Medical Outcomes Study's 12-Item Short-Form Health Survey (SF-12) as a generic core and the 24-item kidney disease targeted questionnaire. The items of the SF-12 are summarized into the Physical Component Summary (PCS) score and the Mental Component Summary (MCS) with response alternatives varying from 2- to 6-point scales. The kidney disease targeted instrument includes three scales: Symptoms and Problems (12 items), Burden of Kidney Disease (4 items), and Effects of Kidney Disease (8 items); all items have 5 response options. The scale scores of the KDQOL-36 questionnaire (PCS, MCS, symptoms and problems, burden of kidney disease, effects of kidney disease,) are transformed to 0 to 100 with higher scores indicating better HRQOL. KDQOL-36 will be administered to adults only and every 12 weeks during Stage 2 placebo-controlled

treatment period. For the SF-12 analysis purpose, the scoring will be provided by QualityMetric Inc, based on Scoring Software Version 4.5 of the SF-12v2 Health Surveys.

- The PedsQL scale is a brief, standardized, generic assessment instrument that systematically assess patients' and parents' perceptions of health-related quality of life in pediatric patients with chronic health conditions. The PedsQL consists of a 23-item core measure, which includes a child self-report for patients aged 5 to 18 years. The 23-item PedsQL Generic Core Scales include four Scales, Physical Functioning (8 items), Emotional Functioning (5 items), Social Functioning (5 items), and School Functioning (5 items).
- The PGIC is a two-item questionnaire (one item evaluating fatigue and the other hearing loss) evaluated on a 7-point Likert scale designed to assess patients' reported evaluation of change in their disease overall in regard to the start of study medication. This aims at evaluating the change in symptoms since the beginning of the study. The participant must select from the response of the options that denotes the most accurate description of his/her change in state of health (overall status) ranging from 'Very much better' to 'Very much worse'.
- The PGIS is a two-item questionnaire (one assessing fatigue and the other hearing loss) evaluated on a 5-point Likert scale designed to assess patients' reported evaluation of severity in their symptoms. The participant must select from the response of the options that denotes the most accurate description of his/her change in state of health (overall status) ranging from 'No [symptom]' to 'Very severe [symptom]'.
- Hearing will be assessed during the Treatment Period and Extension open-label Period using a pure tone audiometry (air only) test at defined frequencies. At baseline, Week 48 and Week 96, hearing will be measured at right and left year. Degrees of hearing level will be derived as follows:
  - All possible hearing results will be converted to numerical value as follows: Normal hearing=0, mild hearing loss=1, moderate hearing loss=2, severe hearing loss=3, profound hearing loss=4.
  - The hearing results from right and left ears will be added up so that degrees of hearing level in both ears ranges from 0 (indicating normal hearing for both ears) to 8 (profound hearing loss for both ears).

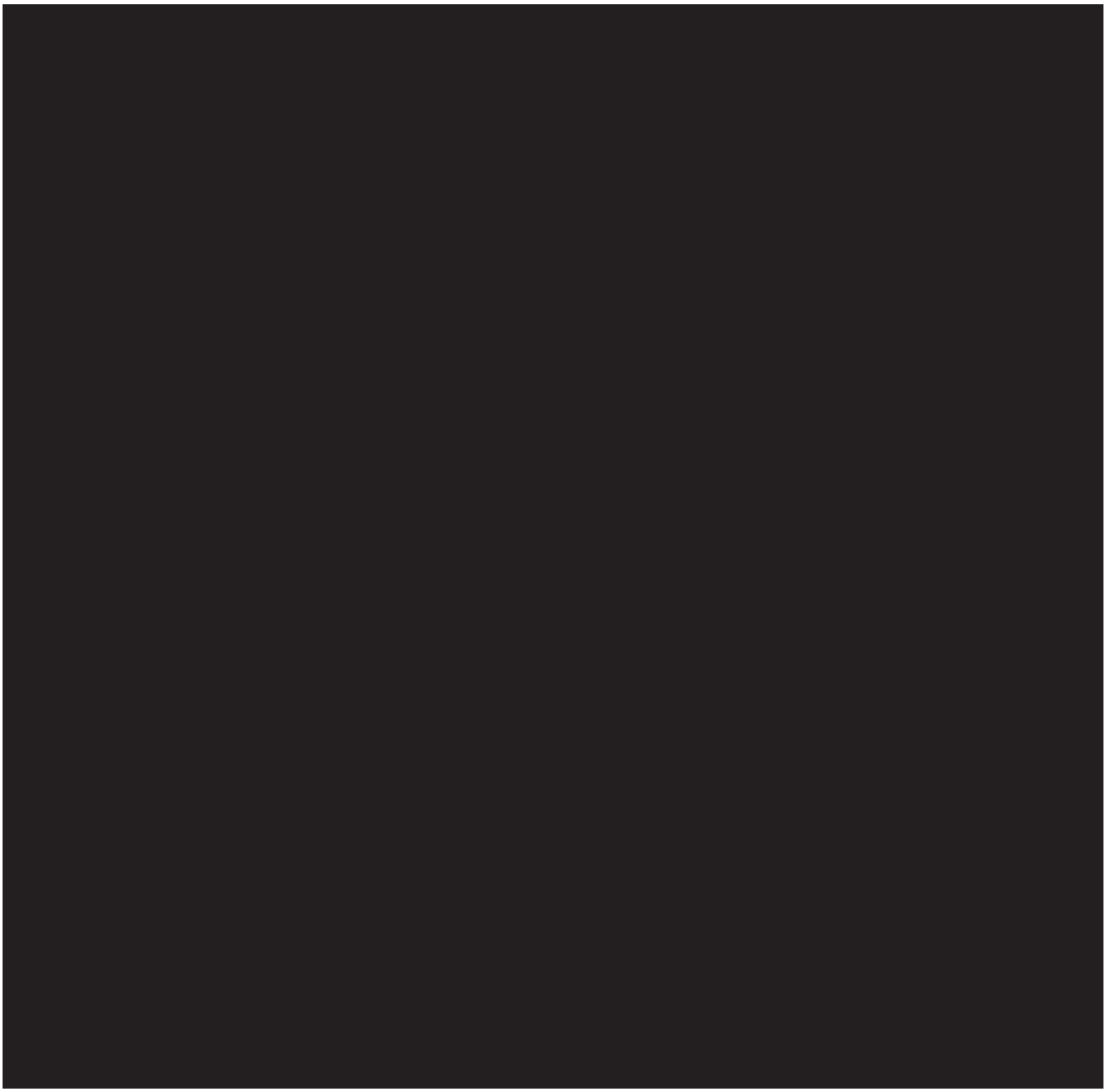
### 4.5.2 Main analytical approach

For the exploratory endpoints that are patient-reported outcomes, the main analytical approaches are discussed in Section 4.8.3. For the tertiary/exploratory biomarker endpoint, the analyses approaches are described in Section 4.8.4. For the rest of the tertiary/exploratory endpoints, the main analytical approaches are described below.

For time to reach the composite endpoint for the secondary population, the same statistical analyses method as described in Section 4.4.1.2.3 will be used. The only exception is that patients with screening eGFR ≤35 mL/min/1.73 $m^2$ will be included.

Change from baseline at Week 48 and Week 96 of double blind placebo-controlled treatment period, respectively in degrees of hearing level recorded in both ears measured by a pure tone audiometry will be analyzed with analysis of covariance (ANCOVA) with treatment, screening eGFR stratification factor, age category (<18 versus ≥18 years old), SGLT2 inhibitor treatment at screening (versus those without) as covariates.

The shift in overall hearing assessment results in both ears (normal hearing, mild, moderate, severe, and profound hearing loss) from baseline to Week 48 and 96 will be summarized.



[redacted]

## 4.7 SAFETY ANALYSES

For safety analyses, other than the analysis for **placebo-controlled treatment** period, the analyses for **lademirsen treatment period** and **overall study treatment period** are discussed both in this section and Section 4.8.5.

### 4.7.1 Extent of exposure

The extent of IMP exposure during placebo-controlled period and overall study period will be assessed and summarized by actual treatment within the safety population. The extent of IMP exposure during lademirsen treatment period will be assessed and summarized by actual treatment within the lademirsen treated population.

#### *4.7.1.1 Extent of investigational medicinal product exposure*

The extent of IMP exposure will be assessed by the duration of IMP exposure and compliance, and actual dose information.

**Duration of IMP exposure**

Duration of IMP exposure in **placebo-controlled period**, will be summarized descriptively as a quantitative variable that number of participants, mean, SD, median, minimum, and maximum will be provided. In addition, duration of treatment exposure will also be summarized categorically by numbers and percentages for each of the following categories and cumulatively according to these categories: >0 and ≤12 weeks, >12 and ≤24 weeks, >24 and ≤36 weeks, ... (by every 12 weeks), and up to the last available study week during the defined treatment period.

Additionally, the cumulative duration of treatment exposure will be provided, defined as the sum of the duration of treatment exposure for all participants in placebo-controlled period, and will be expressed in patient years.

The duration of IMP exposure/cumulative duration of exposure **in lademirsen treatment period** and **in overall study period** will summarized similarly. The following categories of duration of treatment exposure will be presented: >0 and ≤12 weeks, >12 and ≤24 weeks, >24 and ≤36 weeks, ... (by every 12 weeks), and up to the last available study week during the defined treatment period.

#### *4.7.1.2 Compliance*

A given administration will be considered noncompliant if the participant did not take the planned number of administrations as required by the protocol. No imputation will be made for participants with missing or incomplete data.

In **placebo-controlled treatment** period,

- **Percentage of compliance** for a participant is defined as the number of administrations that the participant was compliant (eg, the dose level of actual received is the same as planned) divided by the total number of administrations that the participant was planned during the placebo-control period.
- **Above-planned dosing percentage** for a participant is defined as the number of actual administrations the participants received with a dose level higher than planned (eg, the planned dose is 110 mg for adult however the actual received dose is 120 mg; or the planned dose is 75 mg [=1.5 mg/kg *50 kg] for an adolescent weighted 50 kg, however, the actual received dose is 160 mg) divided by the total number of administrations that the participant was planned during the placebo-control period.

- **Under-planned dosing percentage** for a participant is defined as the number of actual administrations with a lower dose level (eg, the planned dose is 110 mg for adult however the actual received dose is 90 mg or the planned dose is 75 mg [=1.5 mg/kg *50 kg] for an adolescent weighted 50 kg, however, the actual received dose is 100 mg) or even omitted (eg, drug administration at Week xx is planned however not administrated) than planned divided by the total number of administrations that the participant was planned during the placebo-control period.

In **lademirsen treatment** period,

- **Percentage of compliance** for a participant is defined as the number of administrations that the participant was compliant (eg, the dose level of actual is the same as planned) divided by the total number of administrations that the participant was planned to take during the lademirsen treatment period.
- **Above-planned dosing percentage** for a participant is defined as the number of actual administrations the participants received with a dose level higher than planned divided by the total number of administrations that the participant was during the lademirsen treatment period.
- **Under-planned dosing percentage** for a participant is defined as the number of actual administrations with a lower dose level or even omitted (eg, drug administration at Week xx is planned however not administrated) than planned divided by the total number of administrations that the participant was planned during the lademirsen treatment period.

Treatment compliance, above-planned, and under-planned dosing percentages, will be summarized descriptively as quantitative variables (number, mean, SD, median, minimum, and maximum). The percentage of participants whose compliance is <80% and ≥80% will be summarized. In addition, participant numbers and percentages of participants with 0, (0, 20%], and >20% above/under-planned dose administrations will be summarized. All above will be summarized for the analyses during both double-blind treatment period and lademirsen treatment period, respectively.

Number of participants with dose reduction (eg, the schedule of drug administration changed from weekly to bi-weekly) during placebo-controlled treatment period will be summarized in total, by the initiation visit of dose reduction categories as Week 1 - 12, Week 13 - 24, ... (by every 12 weeks), and up to the last available study week during the defined treatment period.

Number of participants with at least one dose omission (eg, drug administration at Week xx is planned however not administrated) during placebo-controlled treatment period will be summarized in total and by the following number of omitted doses categories as 1 - 4, 5 - 8,… (by every 4 doses), and up to maximum allowed dose during the defined treatment period.

The number of participants with dose reduction and at least one dose omission during the lademirsen treatment period will be summarized similarly by extending the categories to the last available study week during the defined treatment period.

A listing of exposure to investigational product of each participant during the overall study period will be provided.

### 4.7.2 Adverse events

*Adverse event observation period*

- **Pre-treatment adverse events** are adverse events that developed or worsened or became serious from the signed informed consent date up to the first administration of IMP.
- **Treatment-emergent adverse events (TEAE)s in placebo-controlled period:** Any adverse events that developed or worsened or became serious during the treatment-emergent placebo-control period.
- **Treatment-emergent adverse events in lademirsen treatment period:** Any adverse events that developed or worsened or became serious during the treatment-emergent lademirsen treatment period.
- **Treatment-emergent adverse events in overall study treatment period:** Any adverse events that developed or worsened or became serious during the treatment-emergent overall study treatment period.

All adverse events will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database extraction or database lock.

**Adverse events of special interest (AESI)**

AESIs reported by the investigator in CRF will be summarized. However, if there are any eGFR grade 2 (toxicity grade 2 or intensity moderate) events retained in the clinical database as AESIs due to reporting based on old AESI grading system of the protocol, they will not be considered as AESIs at the analysis level. Only the reported AESIs which meet the applicable definition at the time of the analysis will be considered at the analysis level.

In addition, lab parameters that potentially meet the criteria in grading system for adverse events of interest table (Table 6) will be summarized separately.

**Table 6 - Grading system for the definition of AESIs**

| Parameter | Mild (Grade 1) | Moderate (Grade 2) | Severe (Grade 3) | Life threatening event (Grade 4) |
|---|---|---|---|---|
| **Platelets** | 125 000 to 100 000 cells/µL | <100 000 to 50 000 cells/µL | <50 000 to 25 000 cells/µL | <25 000 cells/µL |
| **ALT or AST**[a] | 1.25 to <2.5 x ULN | 2.5 to <5.0 x ULN | 5.0 to <10.0 x ULN | ≥10.0 x ULN |
| **Direct Bilirubin** | NA | NA | > ULN with signs and symptoms of hepatotoxicity | > ULN with life-threatening consequences (eg, signs and symptoms of liver failure) |
| **Total Bilirubin** | 1.1 to <1.6 x ULN | 1.6 to <2.6 x ULN | 2.6 to <5.0 x ULN | ≥5.0 x ULN |
| **Alkaline phosphatase** | 1.25 to <2.5 x ULN | 2.5 to <5.0 x ULN | 5.0 to <10.0 x ULN | ≥10.0 x ULN |
| **eGFR**[b] | NA | 10 to <30% decrease from participant's baseline | 30 to <50% decrease from participant's baseline | ≥50% decrease from participant's baseline or dialysis needed |

ALT: alanine aminotransferase; AST: aspartate aminotransferase; eGFR: estimated glomerular filtration rate; NA: not applicable; ULN: upper limit of normal

Grading criteria are based on the DAIDS grading system (1). All deaths related to an AE are to be classified as Grade 5.

*a* For management of elevated aminotransferases, please refer to protocol Section 10.3.2.

*b* If there is any eGFR grade 2 (toxicity grade 2 or intensity moderate) events retain in the clinical database as AESI due to old AESI grading system, they will not be considered as AESI at the analysis level.

For criteria of direct bilirubin Grades 3 and 4 mentioned in Table 6, they are further specified as below:

- Grade 3:
  - Direct bilirubin>ULN + mild to moderate (intensity) Fatigue or/and Nausea or/and Pruritus or/and Oedema peripheral or/and Ascites + Grade 3 (toxicity) Alanine aminotransferase increased or/and Aspartate aminotransferase increased, or
  - Direct bilirubin>ULN + mild to moderate (intensity) Jaundice, or
  - Direct bilirubin>ULN + mild to moderate (intensity) Haemorrhage, or
  - Direct bilirubin>ULN + Grade 3 (toxicity grade) Alanine aminotransferase increased or/and Aspartate aminotransferase increased.
- Grade 4:
  - Direct bilirubin>ULN + severe (intensity) Fatigue or/and Nausea or/and Pruritus or/and Oedema peripheral or/and Ascites + >=Grade 4 (toxicity) Alanine aminotransferase increased or/and Aspartate aminotransferase increased, or
  - Direct bilirubin>ULN + severe (intensity) Jaundice, or
  - Direct bilirubin>ULN + severe (intensity) Haemorrhage, or
  - Direct bilirubin>ULN + Hepatic encephalopathy , or
  - Direct bilirubin>ULN + >=Grade 4 (toxicity) Alanine aminotransferase increased or/and Aspartate aminotransferase increased.

When the ULN for direct bilirubin is not available, 7 umol/L will be used.

To notice that the AEs must happen within 7 days before or concomitant with the event of direct bilirubin >ULN during the same treatment emergent period. For example, if the event of direct bilirubin >ULN happened on October 1, 2021 00:00AM during the placebo-controlled treatment period, only if the mild Haemorrhage started between September 24, 2021 00:00AM (exclusion) to October 1, 2021 00:00AM (inclusion) during the placebo-controlled treatment period, it will be considered as meeting the criteria of Grade 3 direct bilirubin during the placebo-controlled treatment period.

The **primary focus** of adverse event reporting will be on double blind period in placebo-controlled treatment-emergent events on the safety population unless otherwise specified. Key adverse events will also be summarized for the lademirsen treated population in lademirsen treatment period.

***Generalities***

If an adverse event date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the adverse event as pre-treatment and treatment-emergent periods. The algorithm for imputing date/time of onset will be conservative and will classify an adverse event as treatment emergent unless there is definitive information to determine it is not on treatment emergent periods. Details on classification of adverse events with missing or partial onset dates are provided in Section 5.3.

Adverse event incidence tables will present by SOC, and PT, sorted by internationally agreed order of primary SOC and by decreasing incidence of PTs within each SOC, the number (n) and percentage (%) of participants experiencing an adverse event. Multiple occurrences of the same event in the same participant will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the defined population (eg, safety population, lademirsen treated population) within each treatment group. Sorting will be based on results of the lademirsen group if the analysis is on DB TE period or the overall group if the analysis is on lademirsen TE period.

***Analysis of all treatment-emergent adverse events***

- Overview of treatment-emergent adverse events, summarizing number (%) of participants with any
  - Treatment-emergent adverse event,
  - Serious treatment-emergent adverse event,
  - Treatment-emergent adverse event leading to death,
  - Treatment-emergent adverse event leading to dose reduction, and
  - Treatment-emergent adverse event leading to permanent treatment discontinuation.
- All treatment-emergent adverse events, by primary SOC and PT, showing number (%) of participants with at least 1 treatment-emergent adverse event, sorted by internationally

agreed order of primary SOC and by decreasing incidence of PTs within each SOC will be presented.

- All treatment-emergent adverse events related to IMP, by primary SOC and PT, showing the number (%) of participants with at least 1 treatment-emergent adverse event, sorted by internationally agreed order of primary SOC and by decreasing incidence of PTs within each SOC will be presented.
- All treatment-emergent adverse events, by maximal severity, presented by primary SOC and PT, showing the number (%) of participants with at least 1 treatment-emergent adverse event by severity (ie, mild, moderate, or severe), sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC will be presented.
- A listing of all treatment-emergent adverse events during the overall study period will be presented.

***Analysis of all treatment-emergent serious adverse event(s)***

- All treatment-emergent serious adverse events by primary SOC and PT, showing number (%) of participants with at least 1 serious treatment-emergent adverse event, sorted by internationally agreed order of primary SOC and by decreasing incidence of PTs within each SOC will be presented.
- All treatment-emergent serious adverse events related to IMP by primary SOC and PT, showing the number (%) of participants with at least 1 serious treatment-emergent adverse event, sorted by internationally agreed order of primary SOC and by decreasing incidence of PTs within each SOC will be presented.
- A listing of all treatment-emergent serious adverse events during the overall study period will be presented.

***Analysis of all treatment-emergent adverse event(s) leading to permanent treatment discontinuation***

- All treatment-emergent adverse events leading to permanent treatment discontinuation showing the number (%) of participants with permanent treatment discontinuation due to treatment-emergent adverse event, sorted by internationally agreed order of primary SOC and by decreasing incidence of PTs within each SOC will be presented.
- TEAEs leading to permanent treatment discontinuation will be indicated in the listing of TEAEs.

***Analysis of all treatment-emergent adverse event(s) leading to dose reduction***

- All treatment-emergent adverse events leading to dose reduction in placebo-control treatment period showing the number (%) of participants with dose reduction due to treatment-emergent adverse event sorted by internationally agreed order of primary SOC and by decreasing incidence of PTs within each SOC will be presented.
- TEAE leading to dose reduction will be indicated in the listing of TEAEs.

***Analysis of all treatment-emergent adverse events of special interest (AESI)***

- All treatment-emergent AESIs identified by investigator (eg, through eCRF) in placebo-control treatment period showing the number (%) of participants by PT, sorted by the decreasing incidence of PT will be presented.
- AESIs identified by investigator will be indicated in the listing of TEAEs.

***Analysis of treatment-emergent injection site reaction (ISR)***

- Number (%) of participants with treatment emergent injection site reactions by PT by grade/maximal intensity will be provided.

Note: If more than one ISR records (eg, when the ISR grading is >= None [Grade 0]) corresponding to the same adverse event (eg, when the AE code is same) as collected in eCRF, they will be considered as one ISR adverse event during the analysis.

***Analysis of post-treatment adverse events***

- A listing of all adverse events during the post-treatment period may be presented.

***Deaths***

- A listing of all adverse events leading to death during the study will be presented if any.

### 4.7.3 Laboratory variables, vital signs and electrocardiograms (ECGs)

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of all laboratory variables (central laboratory values and changes from baseline) based on availability will be calculated for each visit or study assessments (baseline, each post-baseline time point, last on-treatment during placebo-controlled treatment period and lademirsen treatment period respectively, and worst on-treatment value during placebo-controlled treatment period and lademirsen treatment period respectively) by treatment group during the overall study period.

For selected laboratory parameters (eg, platelet, creatinine, proteinuria [protein/creatinine ratio], albumin/creatinine ratio, eGFR, and selected parameters in liver function), individual participant plots will be prepared for the observed value overtime during overall study period. For selected kidney parameters (eg, cystatin C, and blood urea nitrogen), mean (+/-SE) plots will be prepared for the observed value over time during the double-blind period, and also by screening eGFR stratification factor.

The incidence of PCSAs at any time during the placebo-control treatment-emergent period and lademirsen treatment-emergent period, respectively, will be summarized by biological function and treatment group whatever the baseline level is.

For PCSA analyses, the laboratory measurements obtained at either scheduled or unscheduled visits should be used; and, both the centralized and local test results should be used, as long as their available dates/time is different from each other's. Centralized data will be used

preferentially to the local measures in the PCSA analyses when measurements are performed on the same date and at the same time for a given laboratory test.

Listing of PCSAs during the overall study period will be provided.

#### *4.7.3.1 Lab variables*

Clinical laboratory data consists of hematology, clinical chemistry, and urinalysis. Clinical laboratory values will be converted to both standard international (SI) units and conventional units and may be analyzed in both units.

The laboratory parameters will be classified as follows:

- **Hematology**
  - **Red blood cells and platelets and coagulation**:
    - hemoglobin, hematocrit, red blood cell count, platelet count
    - prothrombin time (PT) and PT expressed as international normalized ratio (INR), fibrinogen, activated partial thromboplastin time (aPTT)
  - **White blood cells:** white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils
- **Clinical chemistry**
  - **Metabolism:**
    - glucose, total protein, albumin
    - total cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), high-sensitivity C-reactive protein (hs-CRP)
  - **Electrolytes**: sodium, potassium, chloride, calcium, phosphorus, bicarbonate, iron
  - **Renal function**: creatinine, cystatin C, blood urea nitrogen, uric acid
  - **Liver function**: total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), and lactate dehydrogenase (LDH)
- **Urine samples**
  - **Urinalysis:** creatinine (quantitate), specific gravity (quantitate from local lab), pH (quantitate from local lab), total protein (qualitative from local lab and quantitate), glucose (qualitative from local lab), ketones (qualitative from local lab), leukocyte esterase (qualitative from local lab and quantitate), nitrate (qualitative from local lab), bilirubin (qualitative from local lab), urobilinogen (qualitative from local lab), urine sediment (qualitative), and hematuria (eg, occult blood, qualitative from local lab)
  - **24-hour urine**: creatinine clearance (quantitate), fractional excretion of sodium (quantitate), total protein (quantitate), total albumin (quantitate), protein/creatinine (quantitate), and microalbuminuria (eg, urine albumin, albumin/creatinine, and albumin excretion rate)

- **Kidney biomarker**: neutrophil gelatinase-associated lipocalin (NGAL)

#### *4.7.3.2 Vital signs variables*

Vital signs: body-temperature, body-weight, systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate

#### *4.7.3.3 Electrocardiogram variables*

12-lead ECGs: the heart rate, PR interval, QRS duration, QT interval, and the Fridercia-corrected QT interval (QTcF).

## 4.8 OTHER ANALYSES

### 4.8.1 PK analyses

Measured plasma concentrations (approximate $C_{max}$ and $C_{trough}$) for lademirsen, RG0005, and SUM (as applicable) will be summarized using descriptive statistics (eg, mean, standard deviation (SD), median, min-max, and coefficient of variation [%CV]. In addition, further PK analysis may be conducted later using a population PK approach. The details of the population PK analysis will be presented in a separate population PK analysis plan and the results will be presented in a separate population PK report.

### 4.8.2 Immunogenicity analyses

Data listings will be provided to display results of anti-drug antibody (ADA). If ADA titer value is reported as <xx, the numeric value will be imputed as xx, the minimum required dilution (MRD), and used for summary purposes. Listing will provide results as reported as well as results as imputed.

A patient with at least one anti-drug antibody response at post-baseline visits in the database is considered evaluable.

A patient whose ADA status is positive at baseline is considered to have **pre-existing ADA**.

A patient whose ADA status is positive anytime post-baseline and is negative or missing at baseline is considered to have **treatment-induced ADA**.

A patient whose ADA status is positive at baseline (pre-existing ADA) and the ADA titer level anytime post-baseline is significantly higher than that at baseline is considered to have **treatment-boosted ADA**. A difference in titer values between 2 samples representing greater than or equal to twice the dilution level is considered significant. In other words, the post-baseline titer value divided by the baseline titer value will be greater than or equal to (≥) 4 to be considered significant. For example, if baseline titer value is 50, the post-baseline titer value has to be ≥200.

For patients with **treatment-induced or treatment-boosted ADA**, the following 3 ADA responses are defined.

**Transient ADA response** is defined as:

- Treatment-induced or treatment-boosted ADA detected at two or more sampling time points post-baseline, where the first and the last ADA-positive samples (irrespective of any negative samples in between) are separated by a period of less than 16 weeks, and the last sample cannot be treatment induced or treatment-boosted.

**Persistent ADA response** is defined as:

- Treatment-induced ADA detected at two or more sampling time points post-baseline, where the first and the last ADA-positive sample (irrespective of any negative samples in between) are separated by at least 16 weeks.

**Indeterminate ADA response** is defined as:

- Only the last sampling time point is positive and all previous samples are negative.

Pre-existing ADA = 100*(Number of patients with pre-existing ADA at baseline)/number of evaluable patients

ADA Incidence = 100*(treatment-boosted + treatment-induced ADA positive patients)/number of evaluable patients

The following summaries will be provided for placebo-controlled treatment period for safety population:

- Number of ADA evaluable patients
- Number (%) of patients with ADA positive/negative at baseline
- Number (%) of patients that never develop ADA at any time (ie, ADA is always negative post-baseline visits )
- Number (%) of patients with treatment-boosted ADA
- Number (%) of patients with treatment-induced ADA
- Treatment emergent ADA: Number (%) of patients with either treatment-boosted or treatment-induced ADA
- Duration of ADA response: Number (%) of patients with transient/persistent/indeterminate ADA response (each category will be analyzed separately)
- Patients with treatment-induced ADA will be further characterized
  - Peak ADA titer: Median, $25^{th}/75^{th}$ quantiles, min, max of the ADA titer for peak ADA titer of treatment-induced ADA positive patients
  - Last ADA titer (final assessment): Median and 25th/75th quantiles, min, max of the last ADA titer of treatment induced ADA positive patients

The same summaries will also be provided for **lademirsen treated population** in the **lademirsen treatment period** where baseline will be the last non-missing measure prior to first infusion of lademirsen. The details are discussed in Section 4.8.5.

### 4.8.3 Patient-reported outcomes analyses

The analysis for the secondary endpoint symptom measure of FACIT-F is already described in Section 4.4.1.2.4. This section describes the analyses for the quality of life measures and Patient-reported outcomes that are not secondary endpoints.

***Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scales***

For the percentage change in fatigue, as measured by FACIT-F scales at Week 96 of placebo-controlled period for Stage 2 primary population, the same analyses method as summarized in Section 4.4.1.2.4 will be used with the exception that all data up to Week 96 will be included.

Percentage of participants experiencing a meaningful worsening of their fatigue as measured by FACIT-F scales total score at Week 96 will be determined use the same approach as summarized in Section 4.4.1.2.4. The binary measure of responder (yes vs no) at Week 96 separately will be analyzed with same logistic regression method as described in Section 4.4.1.2.4.

***KDQOL-36***

The change from baseline at Week 48 and 96 on health related quality of life measure by KDQOL-36 for adults, will be analyzed using the MMRM model described in Section 4.4.1.2.4 with the exception the following exceptions:

- Age category will not be in the model.
- At interim analysis 3, only data up to Week 48 will be included,
- At final analysis, all data up to Week 96 will be included.

For KDQOL analyses, the scoring will be provided by KDQOL-SF™v1.3 scoring manual.

***PedsQL General core scales***

The change from baseline at Week 48 and 96 on health related quality of life measure by PedsQL General core scales for adolescents aged 12 to <18 years respectively, will be analyzed using the MMRM model described in Section 4.4.1.2.4 with the exception the following exceptions:

- Age category will not be in the model.
- At interim analysis 3, only data up to Week 48 will be included,
- At final analysis, all data up to Week 96 will be included.

The PedsQL consists of a 23-item core measure, which includes a child self-report for patients aged 5 to 18 years. The 23-item PedsQL Generic Core Scales include four Scales, Physical Functioning (8 items), Emotional Functioning (5 items), Social Functioning (5 items), and School Functioning (5 items).

1. On the PedsQL Generic Core Scales, for ease of interpretability, items are reversed scored and linearly transformed to a 0-100 scale, so that higher scores indicate better Health-Related Quality of Life.
2. To reverse score, transform the 0-4 scale items to 0-100 as follow:

   0=100, 1=75, 2=50, 3=25, 4=0.
3. To create Scale Scores, if more than 50% of the items in the scale are missing, the Scale Score will not be computed. If 50% or more of the items in the scale are completed, compute the Scale Score using the sum of non-missing items scores divided by the number of items answered.
4. The PedsQL Generic Core Scales for ages 5-18 years: to create the Psychosocial Health Summary Score, the mean is computed as the sum of the items scores over the number of items answered in the Emotional, Social, and School Functioning Scales; the Physical Health Summary Score is the same as the Physical Functioning Scale Score.
5. To create the Total Scale Score, the mean is computed as the sum of all the items scores over the number of items answered on all the Scales.

| Response Choices | Never | Almost Never | Sometimes | Often | Almost Always |
|---|---|---|---|---|---|
| Raw Scores | 0 | 1 | 2 | 3 | 4 |
| 0-100 Scale Scores | 100 | 75 | 50 | 25 | 0 |

Scale Scores, Psychosocial Health Summary Score, Physical Health Summary Score and the Total Scale Score will be calculated based on the 0-100 scale scores. Their computed values and changes from baseline will be summarized by age group cohorts at each scheduled time point.

***PGIS/PGIC***

For PGIC, 7 categories of response will be converted to the following numeric values:

- Very much Better = 3
- Moderately Better = 2
- A Little Better = 1
- No Change = 0
- A Little Worse = -1
- Moderately Worse = -2
- Very much Worse =-3

Observed numeric values at each post-baseline visits will be analyzed using MMRM model described in Section 4.4.1.2.4 with the exception that at the 3rd interim analysis, only data up to Week 48 will be included, and at final analysis, all data up to Week 96 will be included. And in the MMRM model, the baseline value will be PGIS at screening with value of 0=none, 1=mild, 2=moderate, 3=severe, 4=very severe.

The PGIS at baseline and post-baseline visits will be converted to a numeric score on 0-4 scale (0=no fatigue, 1=mild fatigue, 2=moderate fatigue, 3=sever fatigue, 4=very severe fatigue). Therefore, change from baseline at each post-baseline visits using MMRM model described in Section 4.4.1.2.4 with the exception that at interim analysis 3, only data up to Week 48 will be included, and at final analysis, all data up to Week 96 will be included.

### 4.8.4 Pharmacodynamic and Biomarker analyses

***Supportive secondary biomarker endpoints***

Change in circulating miR-21, kidney injury and function biomarkers from baseline at Weeks 24 and 48 (using both Stage 1 and Stage 2 data), and Week 96 (using Stage 2 data only) during the placebo-controlled treatment period for primary population

- Circulating miR-21
- In blood only: blood urea nitrogen (BUN)
- In urine only: protein/creatinine ratio (UPCR), albumin/creatinine ratio, and epidermal growth factor (EGF)
- In both blood and urine: creatinine, Cystatin C, transforming growth factor-β (TGF-β), and neutrophil gelatinase-associated lipocalin (NGAL)

***Exploratory biomarker endpoints***

Change in exploratory biomarkers from baseline at Weeks 48 (using both Stage 1 and Stage 2 data) and Week 96 (using Stage 2 data only), which may include but are not necessarily limited to:

- In blood only: microRNAs (miRs) other than miR-21
- In both blood and urine: β-2 microglobulin and connective tissue growth factor (CTGF)
- In urine only: kidney injury molecule-1 (KIM-1) and calbindin-D28k

No exploratory biomarkers will be evaluated for Chinese participants. The following assessments will not be evaluated for Chinese participants: β2-microglobulin, calbindin‑D28k, CTGF, microRNAs (other than miR-21, as listed above), and KIM-1.

All the above biomarkers will be analyzed using primary population (excluding Chinese participants where exploratory biomarkers were not evaluated). Observed, change from baseline values and percent change from baseline values will be summarized at scheduled visits. Summary plots of the mean values over time for some of the biomarker endpoints may be provided if deemed necessary.

### 4.8.5 Analyses for placebo controlled and open label treatment period combined

The observation periods for analyses for placebo controlled and open label treatment period combined are defined in Section 4.1:

***Analyses for Efficacy, Patient-reported outcomes and pharmacodynamic/biomarker endpoints***

All of the efficacy, Patient-reported outcomes and pharmacodynamic/biomarker endpoints throughout the whole study including all longitudinal time points from both placebo-controlled, and open label treatment period will be summarized by randomized treatment groups, using **primary population** and the same baseline definition for both randomized treatment groups (latest observation prior to the first infusion of the IMP in the study). For those analyses, descriptive statistics will be provided. Data in Stage 1 and Stage 2 will be analyzed separately as well as combined, thus the 6 columns will be displayed in the table header, "Stage 1 placebo, Stage 1 lademirsen, Stage 2 placebo, Stage 2 lademirsen, Pooled Placebo, Pooled Lademirsen". Except for analysis on Patient-reported outputs, they will be analyzed as Stage 2 lademirsen and Stage 2 placebo since those measurements were collected at Stage 2 only. No difference between treatment comparison will be provided.

eGFR slope will also be estimated with the same model as summarized in Section 4.3.2 for **lademirsen treated population in lademirsen treatment period** by randomized treatment group and overall using all the eGFR data while on lademirsen.

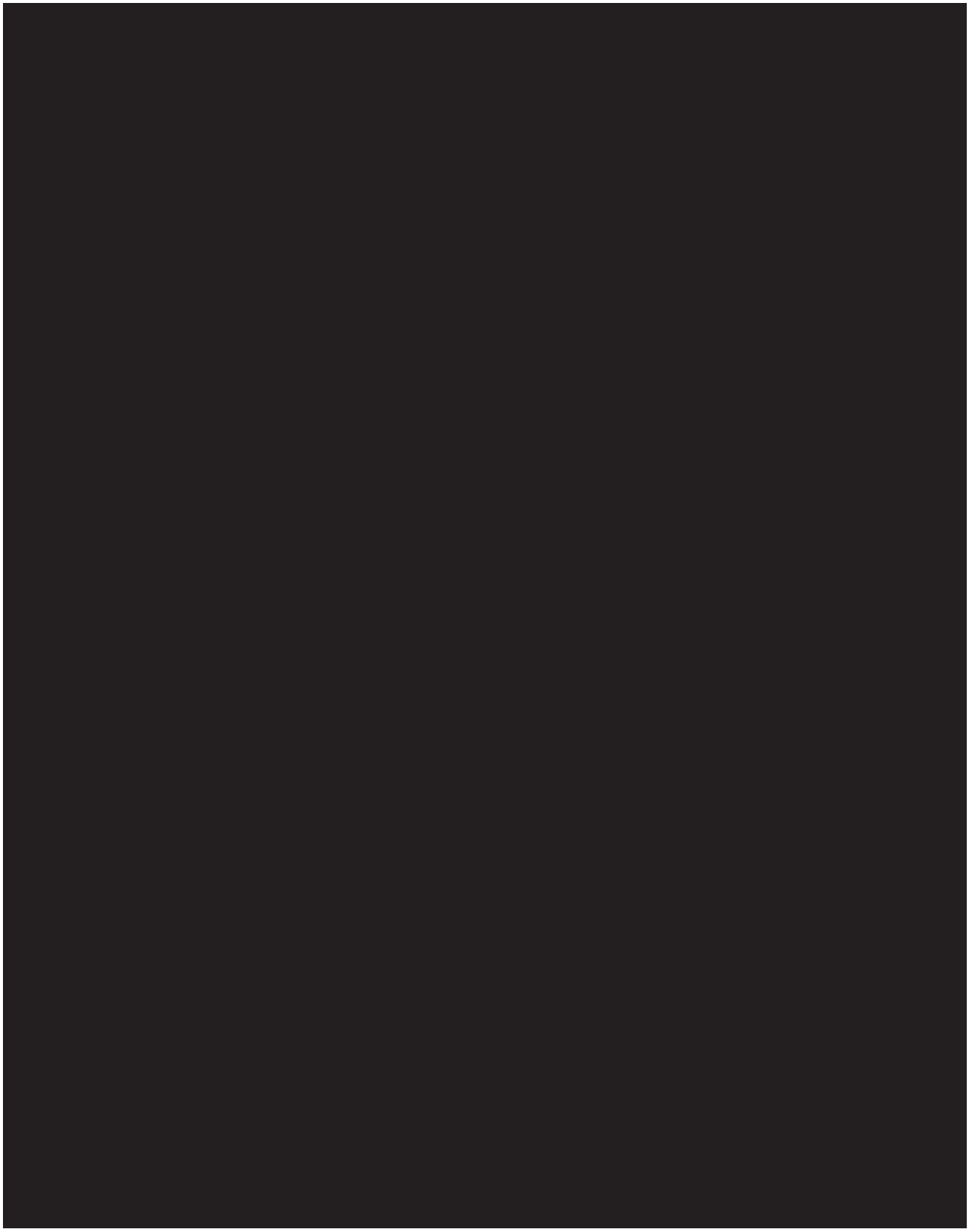
Time to reach composite endpoint (as defined in Section 4.4.1.1) for **lademirsen treated population in lademirsen treatment period** will also be summarized using Kaplan-Meier estimate. For this analysis, time to reach composite endpoint will be defined as time from first infusion of lademirsen treatment to first reaching composite endpoint. Subjects who have not reach composite endpoint will be censored at the last available day in the study.

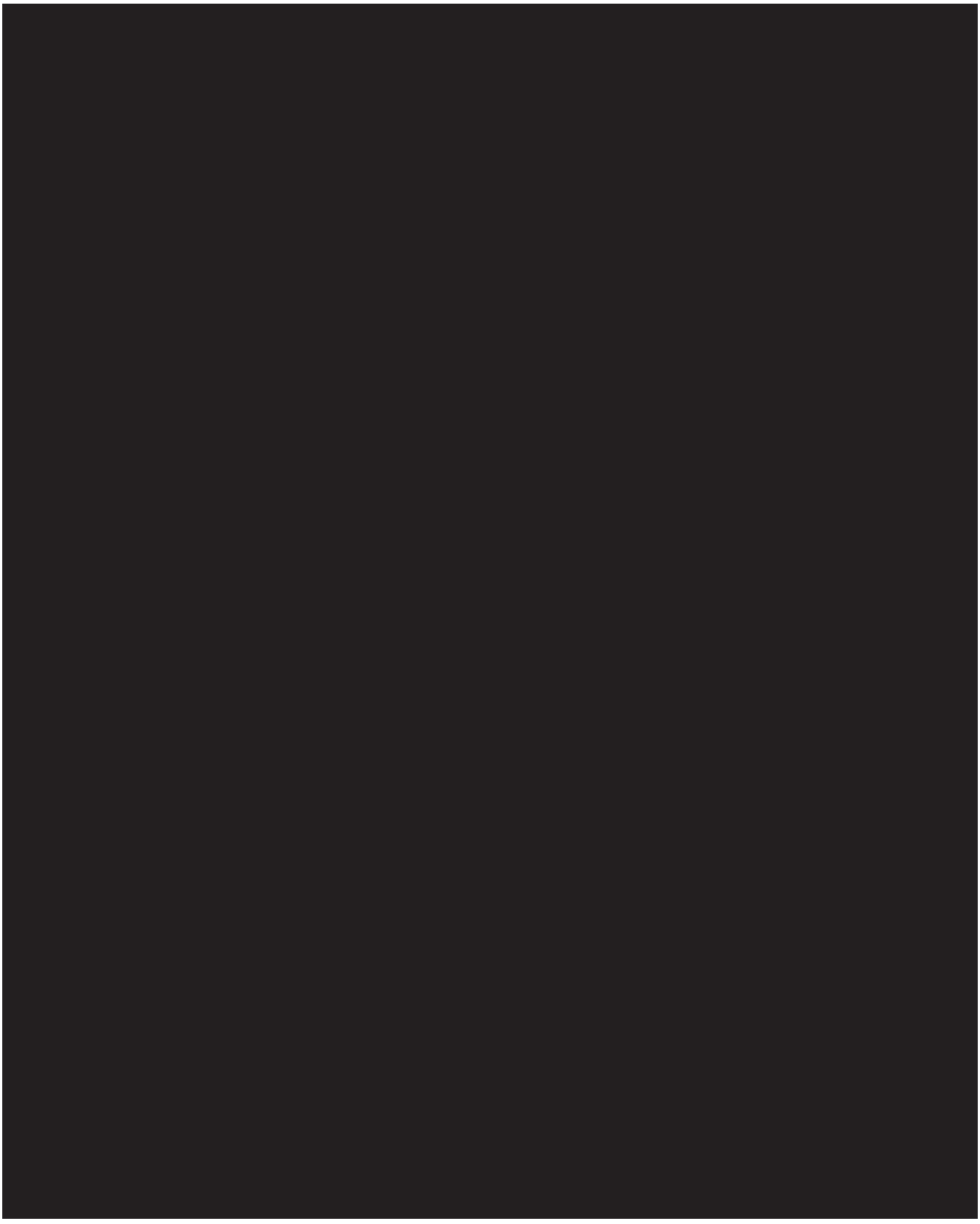
Summary plots and by-patient plots will be provided as appropriate.

***Analyses for safety and immunogenicity endpoints***

For categorical measures, such as AE, PCSA analyses, ADA and neutralizing ADA incidence, data throughout both placebo-controlled and open label extension period during lademirsen exposure will be summarized as an overall group for **lademirsen treated population in lademirsen treatment period**:

For continuous measures collected at longitudinal time point, such as labs and vital signs, data throughout both placebo-controlled and open label period will be summarized as at each longitudinal time point for **safety population**. The baseline will be defined as the last non-missing value prior to first infusion of IMP at placebo-controlled period. For those analyses, data in Stage 1 and Stage 2 will be analyzed separately as well as combined, thus the 6 columns will be displayed in the table header, "Stage 1 placebo, Stage 1 lademirsen, Stage 2 placebo, Stage 2 lademirsen, Pooled placebo, Pooled lademirsen".





# 5 SUPPORTING DOCUMENTATION

## 5.1 APPENDIX 1 LIST OF ABBREVIATIONS

| | |
|---|---|
| ACEi: | angiotensin-converting enzyme inhibitor |
| ADA: | anti-drug antibody |
| AEs: | adverse events |
| ARB: | angiotensin II receptor blocker |
| CKD-EPI: | chronic kidney disease epidemiology collaboration |
| CTGF: | connective tissue growth factor |
| ECG: | 12-lead electrocardiogram |
| EGF: | epidermal growth factor |
| eGFR: | estimated glomerular filtration rate |
| IA: | interim analysis |
| IMP: | investigational medicinal product |
| KIM-1: | kidney injury molecule-1 |
| miRs: | microRNAs |
| NGAL: | neutrophil gelatinase-associated lipocalin |
| PGIC: | patients' global impression of change |
| PGIS: | patient's global impression of severity |
| QW: | every week |
| SAEs: | serious adverse events |
| SC: | subcutaneous |
| SD: | standard deviation |
| SGLT2: | Sodium-glucose Co-transporter 2 |
| TEAE: | treatment-emergent adverse event |
| TGF-β: | transforming growth factor |

## 5.2 APPENDIX 2 DEMOGRAPHIC AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

### 5.2.1 Demographic and baseline characteristics

The baseline value is defined generally as the last available value before the first dose of double-blind investigational medicinal product (IMP). For participants randomized but not treated, the baseline value is defined as the last available value before randomization.

For participants who are randomized to placebo and complete the double-blind, placebo-controlled treatment period and choose to enter the open-label treatment extension, the last available value before the first dose of lademirsen will serve as the baseline value **for the analyses during lademirsen treatment period on lademirsen treated population**.

All baseline safety and efficacy parameters (apart from those listed below) are presented along with the post-baseline summary statistics in the safety section (Section 4.7).

***Demographic characteristics***

Demographic variables are age in years, age in category of <18 and ≥18 years (will be displayed after the Stage 2 participants are randomized), gender (Male, Female), race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Island, multiple, unknown, Not reported [if race is missing]), country (Australia, China, France, Germany, Spain, United Kingdom, United States), ethnicity (Hispanic or Latino, not Hispanic or Latino, not reported, unknown), Weight (kg), Height (cm) and BMI ($kg/m^2$).

***Medical or surgical history***

Medical (or surgical) history includes participant's significant prior (eg, occurring before signing the ICF) and ongoing illnesses, surgeries, and smoking history. Medical and surgical history will be coded to a LLT, PT, HLT, HLGT, and associated primary SOC using the MedDRA version currently in effect at Sanofi at the time of database lock or data snapshot.

***Family medical history***

Family history relevant to Alport syndrome and renal disease will be collected and summarized.

***Disease characteristics at baseline***

- Age at diagnosis of Alport syndrome (years)
- Time from diagnosis of Alport syndrome to randomization (years)
- Type IV collagen alpha chain gene (COL4A3/4/5) genotyping
- Baseline eGFR value (quantitative and qualitative: ≤35 mL/min/1.73 $m^2$, >35 to <60 mL/min/1.73 $m^2$ versus ≥60 mL/min/1.73 $m^2$)
- Slope of eGFR values (mL/min/1.73$m^2$/year) up to screening if available
- Slope of eGFR values (mL/min/1.73$m^2$/year) up to screening if the participants meeting protocol inclusion criteria I05A
- Proteinuria:
  - urine protein-to-creatinine ratio (mg/g)
  - urine albumin-to-creatinine Ratio (mg/g)
- Hearing test result for each ear

***Disease characteristics of ACEi/ARB usage***

- Prior medication of ACEi/ARB usage (Yes/No)
- Concomitant medication of ACEi/ARB usage during the study (Yes/No)
- Length (in year) of concomitant medication of ACEi/ARB usage during the study (the length is calculated from the first ACEi/ARB usage in the study to the last study day during on-treatment period if the participant didn't discontinue the medication; or from the

first ACEi/ARB usage in the study to the last ACEi/ARB usage during the on-treatment period if the participant discontinued the medication)

***Disease characteristics of SGLT2 inhibitor usage (this will be provided when Stage 2 participants are randomized)***

- Prior medication of SGLT2 ***inhibitor*** usage (Yes/No)
- Concomitant medication of SGLT2 inhibitors usage during the study (Yes/No)
- Length (in year) of concomitant medication of SGLT2 inhibitor usage during the study (the calculation method is similar to ACEi/ARB)

### 5.2.2 Prior or concomitant medications

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database extraction or database lock.

- Prior medication/therapy is any medication or therapy given within 30 days before study entry (eg, given within 30 days before signing the ICF/and assent for adolescent) and up to the first IMP intake. Concomitant medications are any interventions received by the participant concomitantly to the IMP during the defined on-treatment periods.
- A given medication can be classified both as a prior medication and as a concomitant medication.

The medications of ACEi/ARB are identified by ATC code C09 (Agents acting on the renin-angiotensin system).

The medications of SGLT2 inhibitors are identified by ACT code A10BK (sodium-glucose co-transporter 2 [sglt2] inhibitors).

For participants who received ACEi/ARB during the study or as prior medication, the medication's information including medication coded name, start and stop date (if available) of medication will be presented in a listing.

The same listing will be provided for participants whom received SGLT2 inhibitors.

## 5.3 APPENDIX 3 DATA HANDLING CONVENTIONS

For analyses of all the primary, secondary and exploratory endpoints during placebo-controlled treatment period, with the exception for the endpoints only collected at Stage 2, data from both Stage 1 and Stage 2 data will be included for the analyses.

***Derivation of "year" for eGFR slope analysis***

Year of each eGFR measurement relative to the first IMP injection is calculated as (date of eGFR measurement - the first IMP injection date +1) divided by 365.25. Specially, for the last non-missing eGFR measure collected prior to first IMP injection, it will be coded to year=0.

***Missing data handling for eGFR***

The primary analysis will include all data collected in Primary Population, regardless of whether or not subjects completed the treatment period. Subjects who prematurely and permanently discontinue study medication will be requested to enter 10 weeks post-treatment follow up period. Data collected during those 10 weeks post-treatment period will be included in the primary analysis up to 48 weeks for Stage 1 data, and up to 96 weeks for Stage 2 data.

All efforts will be made to minimize the amount of missing data. eGFR data is scheduled to be collected at baseline, Week 2, Week 4, and every 4 weeks thereafter. However, if data was not collected at the scheduled visits, every possible effort should be made to collect the data at next possible unscheduled visits, and a corresponding week will also be assigned for those unscheduled visits for analysis purpose. For example, if a subject cannot come for a scheduled visit at Week 16, then an unscheduled visit between Week 16 and Week 20 should be planned, and if this unscheduled visit happens on Week 18, then Week 18 data will be used for the analysis.

***Demographic formulas***

Age at diagnosis of Alport syndrome is calculated as:

(Date of diagnosis of Alport syndrome [yyyy-mm-dd] - Date of informed consent or assent for adolescent [yyyy-mm-dd])/365.25 + Age at informed consent or assent for adolescent

Time from diagnosis of Alport syndrome (years) is calculated as:

(Date of randomization [yyyy-mm-dd] - Date of diagnosis of Alport syndrome [yyyy-mm-dd])/365.25

For the dates used in the above calculations, if month is missing, it will be imputed to June; and if the day is missing, it will be imputed to the $15^{th}$.

***Handling of missing data for categorical variable***

For categorical variables, participants with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of participants with missing data is presented.

***Handling of computation of treatment duration if investigational medicinal product end of treatment date is missing***

For the calculation of the treatment duration, the date of the last dose of IMP is equal to the date of last administration reported on case report form - exposure single dose page.

The last dose intake should be clearly identified in the case report form and should not be approximated by the last returned package date.

***Handling of medication missing/partial dates***

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant, and post-treatment medication.

***Handling of adverse events with missing or partial date/time of onset***

Missing or partial adverse event onset dates and times will be imputed so that if the partial adverse event onset date/time information does not indicate that the adverse event started prior to treatment or after the treatment-emergent adverse event period, the adverse event will be classified as treatment-emergent. Further, if the double-blind period or open-label period cannot be determined, then this AE will be considered as a TEAE started during double-blind period. No imputation of AE end dates/times will be performed. No imputation of adverse event end dates/times will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of adverse event resolution.

***Handling of adverse events when date and time of first investigational medicinal product administration is missing***

When the date and time of the first IMP administration is missing, all adverse events that occurred on or after the day of randomization should be considered as double-blind placebo-controlled treatment period treatment-emergent adverse events. The exposure duration should be kept as missing.

The last dose intake should be clearly identified in the case report form and should not be approximated by the last returned package date.

***Handling of missing assessment of relationship of adverse events to investigational medicinal product***

If the assessment of the relationship to IMP is missing, then the relationship to IMP has to be assumed and the adverse event considered as such in the frequency tables of possibly related adverse events, but no imputation should be done at the data level.

***Handling of missing severity/grades of adverse events***

If the severity/grade is missing for one of the double-blind placebo-controlled treatment period treatment-emergent occurrences of an adverse event, the maximal severity on the remaining double-blind placebo-controlled treatment period occurrences will be considered. If the severity/grade is missing for one of the open-label treatment extension period treatment-emergent occurrences of an adverse event, the maximal severity on the remaining open-label treatment extension period occurrences will be considered. If the severity is missing for all the occurrences, a “missing” category will be added in the summary table.

***Handling of potentially clinically significant abnormalities***

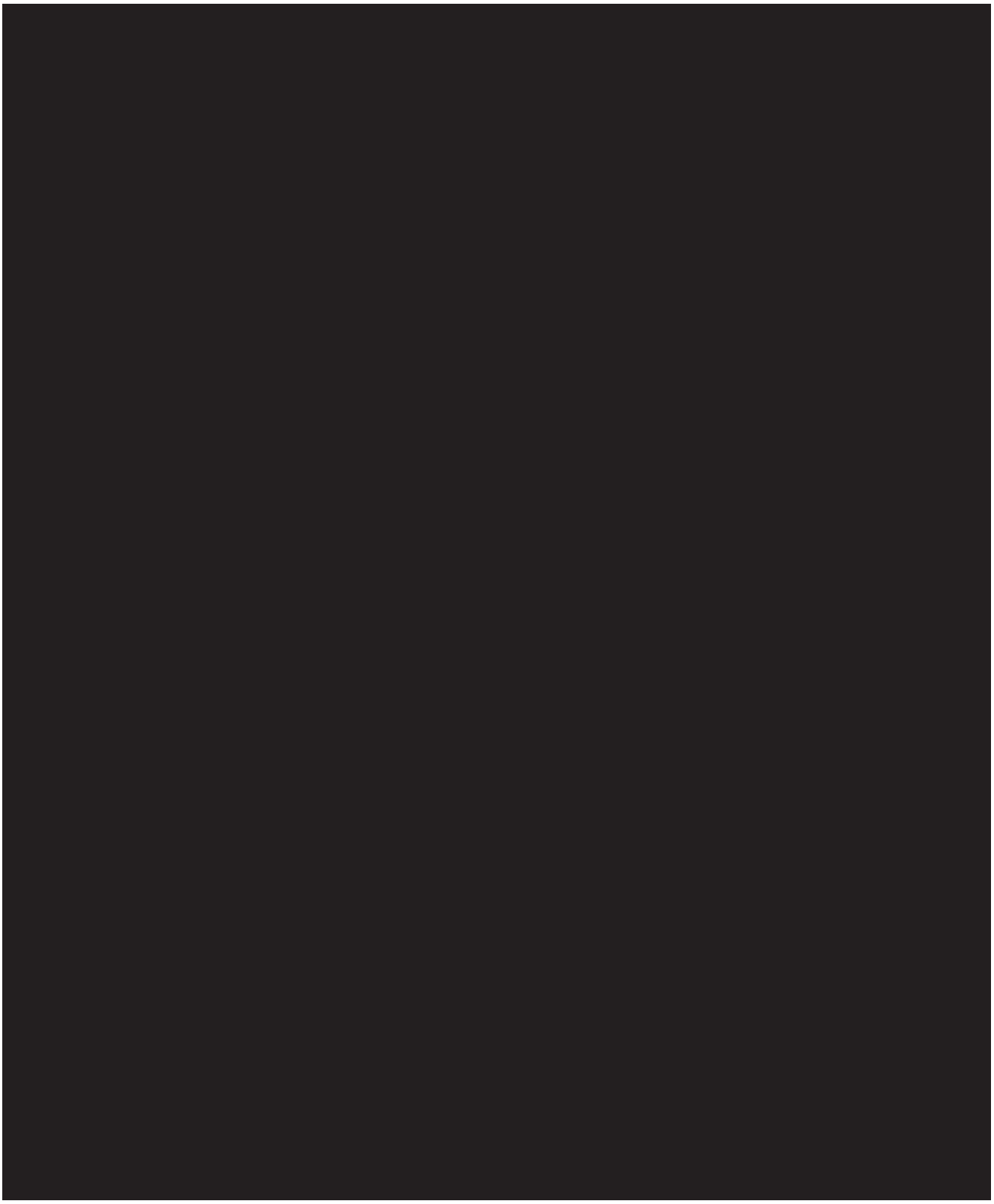
For PCSAs with 2 or more conditions, eg, one based on change from baseline value or a normal range and the other on a threshold value, the PCSAs will be analyzed only when both baseline and post-baseline are available.

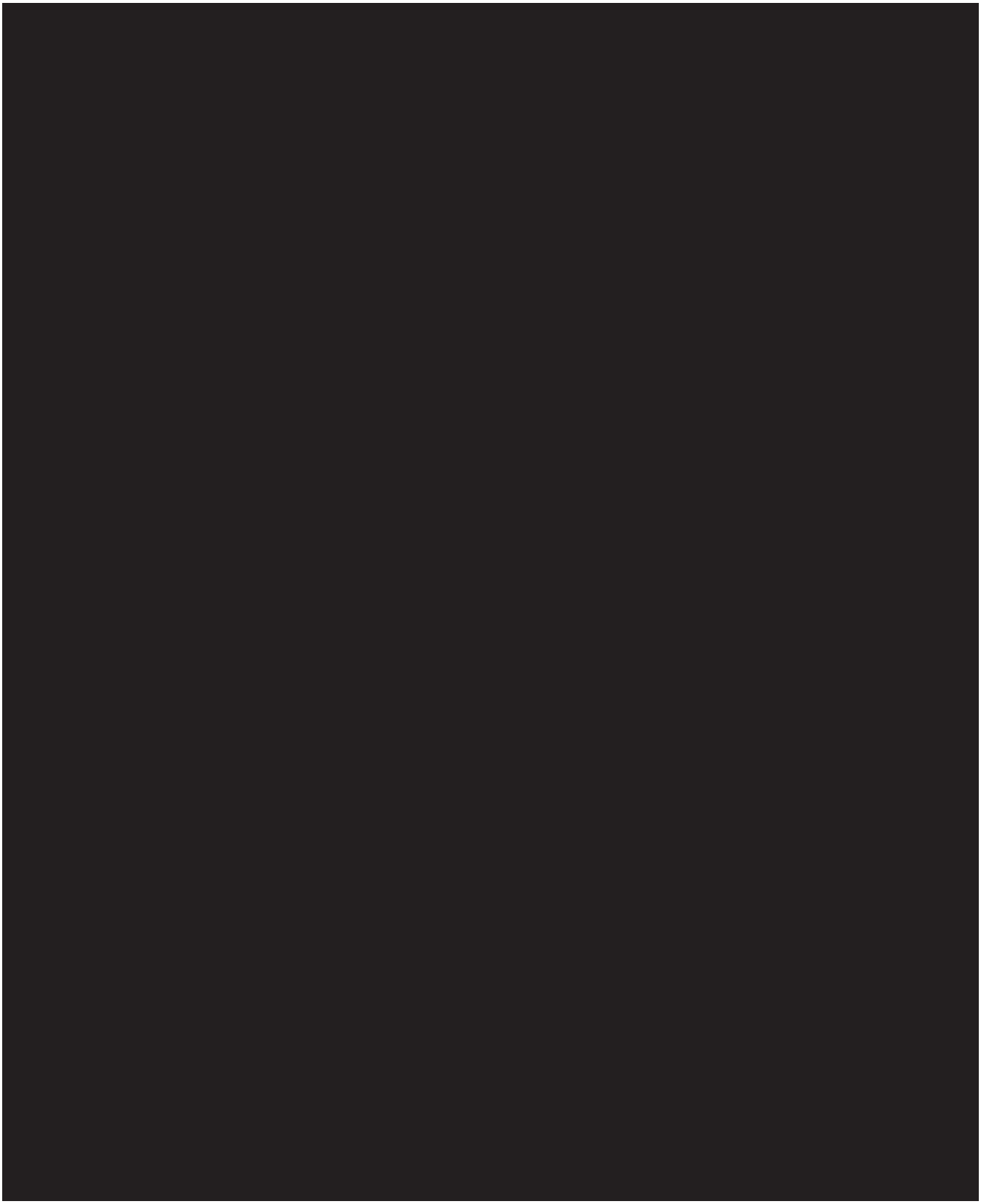
For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing; eg, for eosinophils the PCSA is > 0.5 GIGA/L or >ULN if ULN ≥0.5 GIGA/L. When ULN is missing, the value 0.5 should be used.

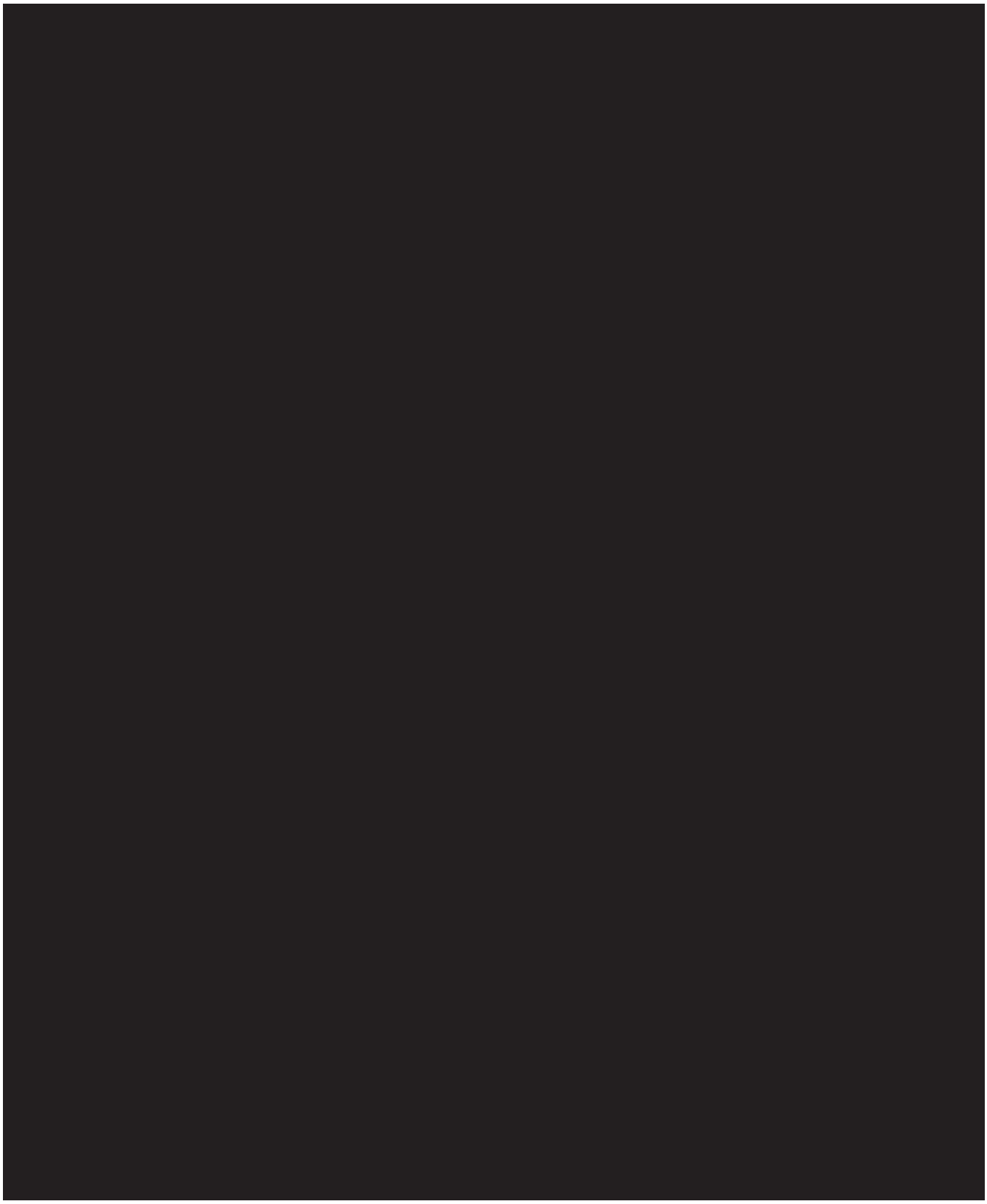
Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSA values.

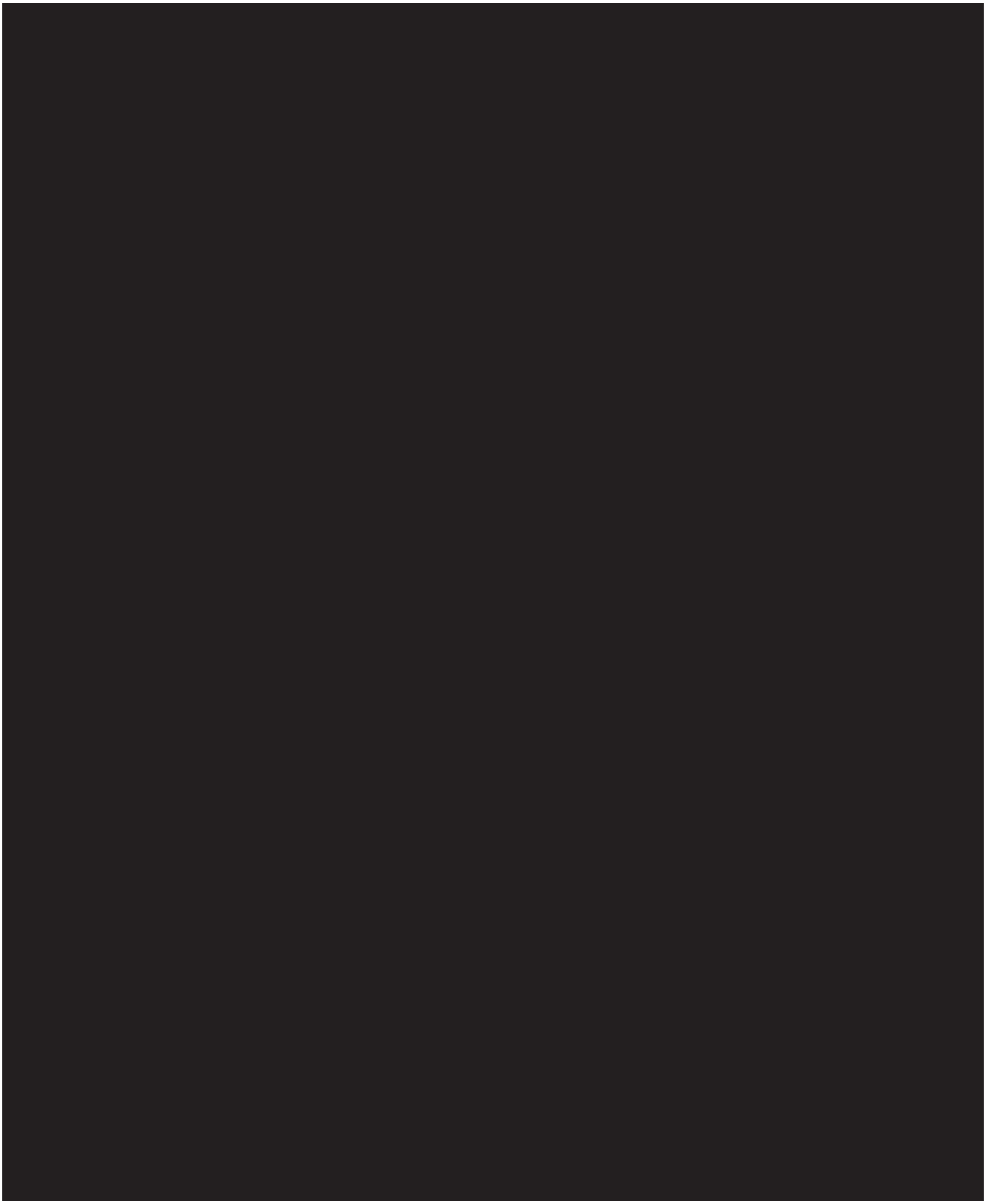
***Unscheduled visits***

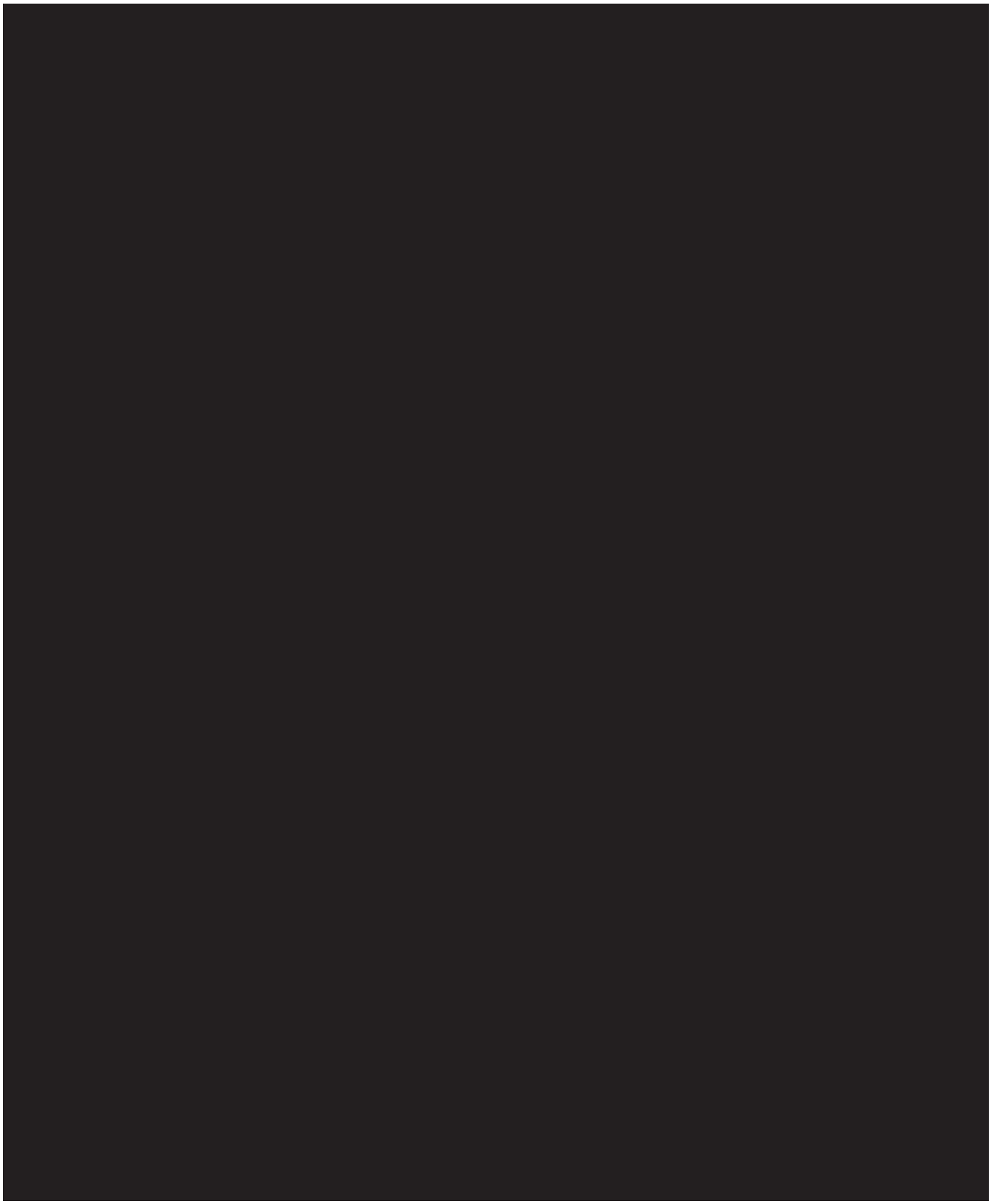
Unscheduled visit measurements of laboratory data, vital signs, and ECG will not be included in the by-visit summaries unless they are re-allocated to scheduled visits. However, the unscheduled visits will be used for computation of baseline, worst values, the last on-treatment value, and PCSAs.

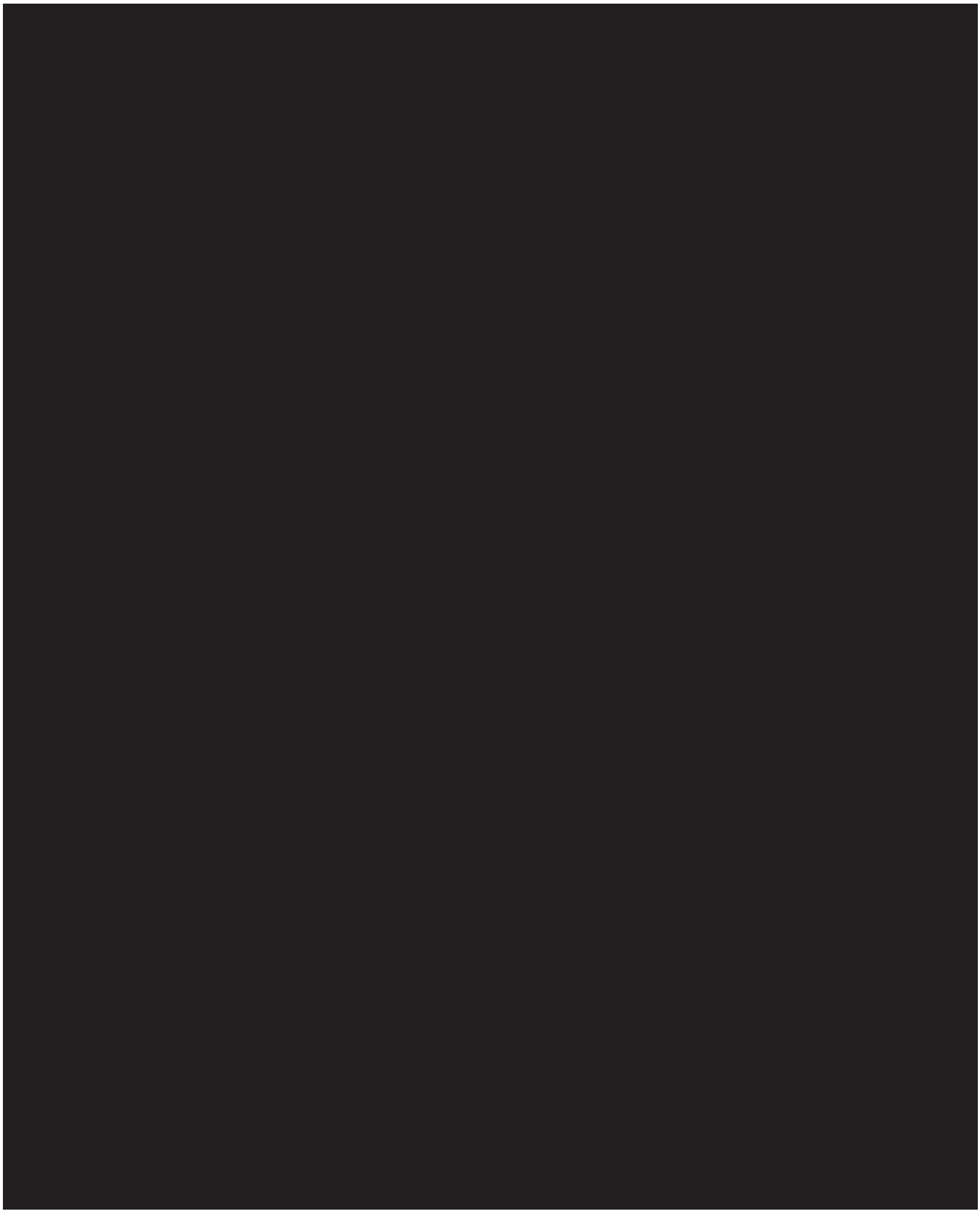


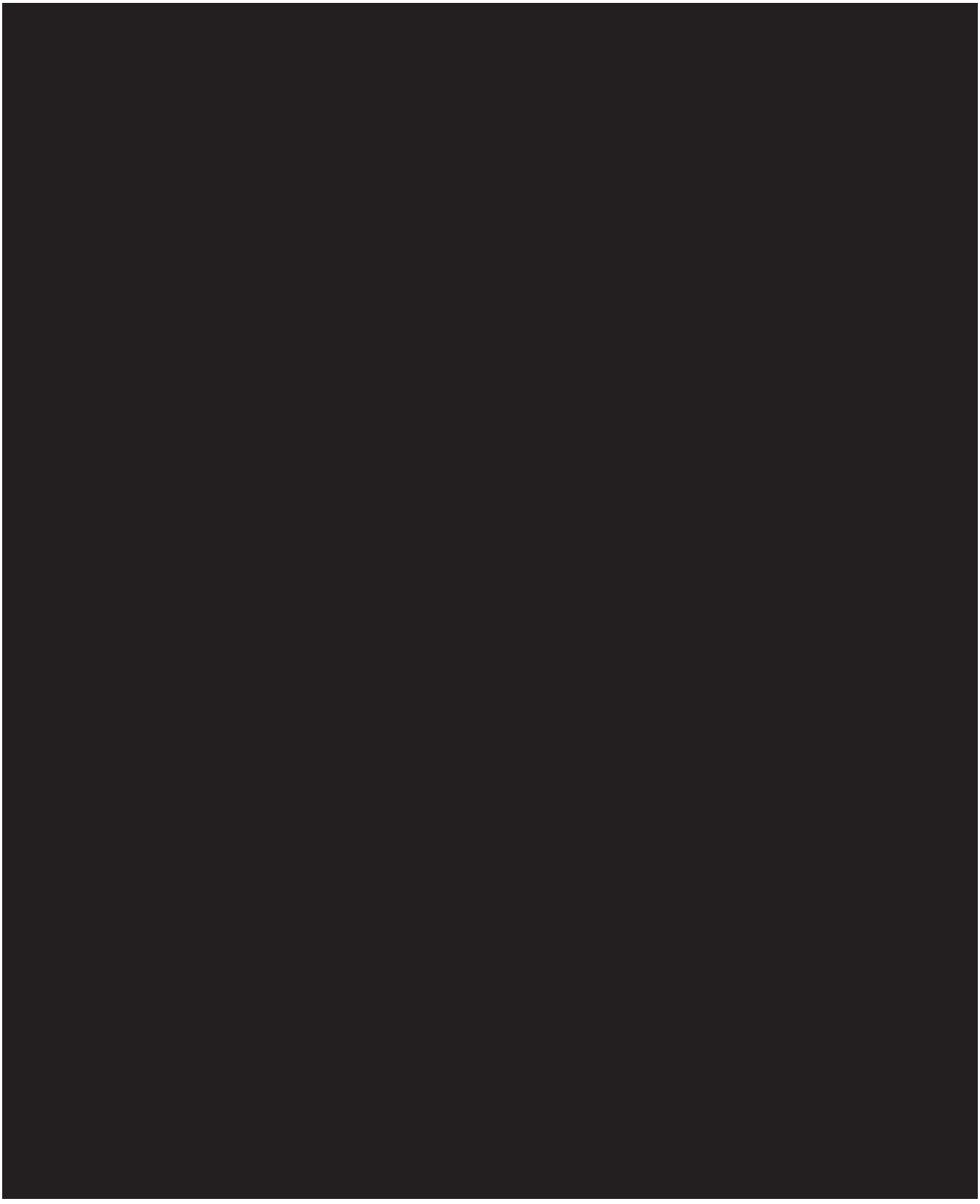


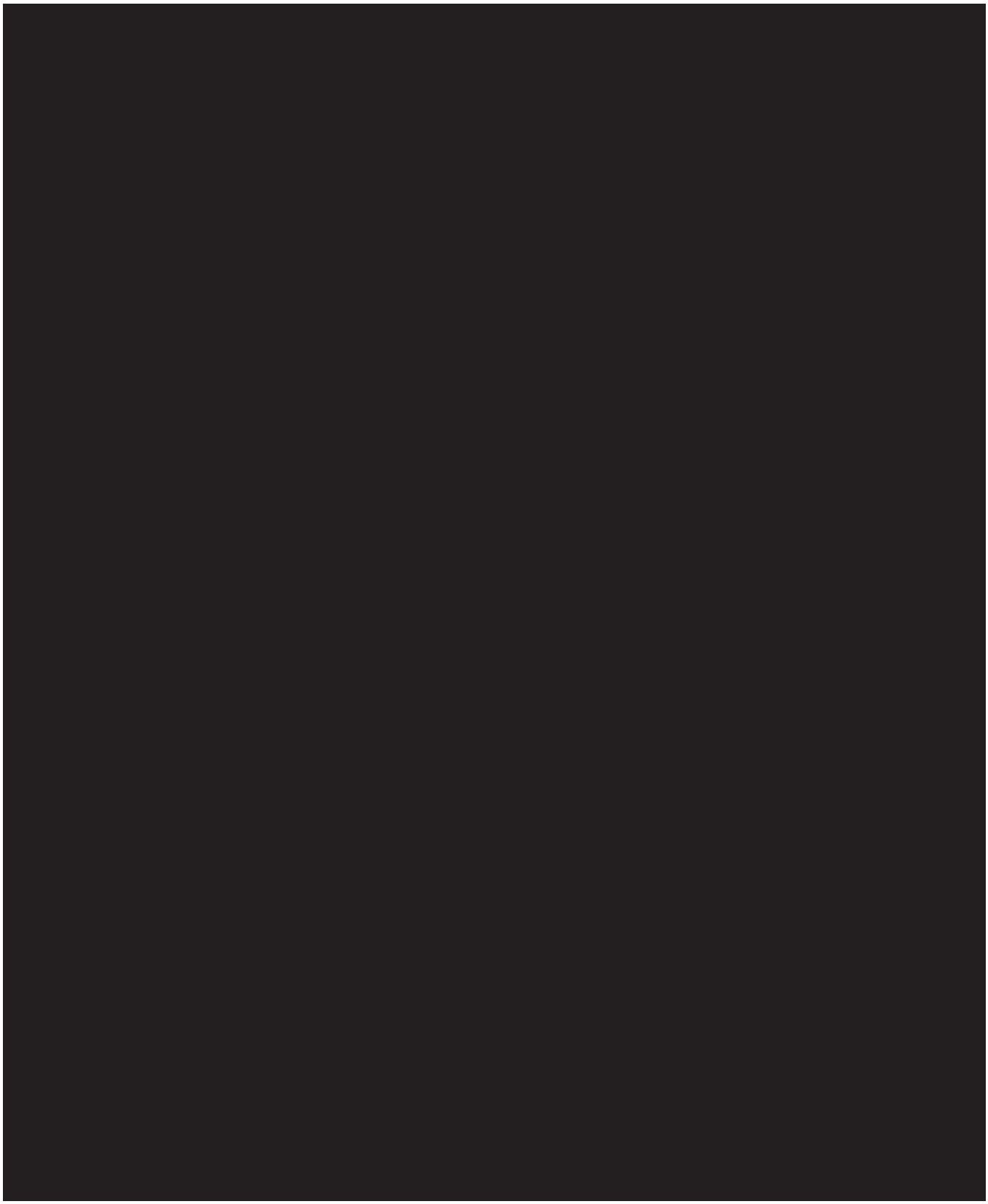


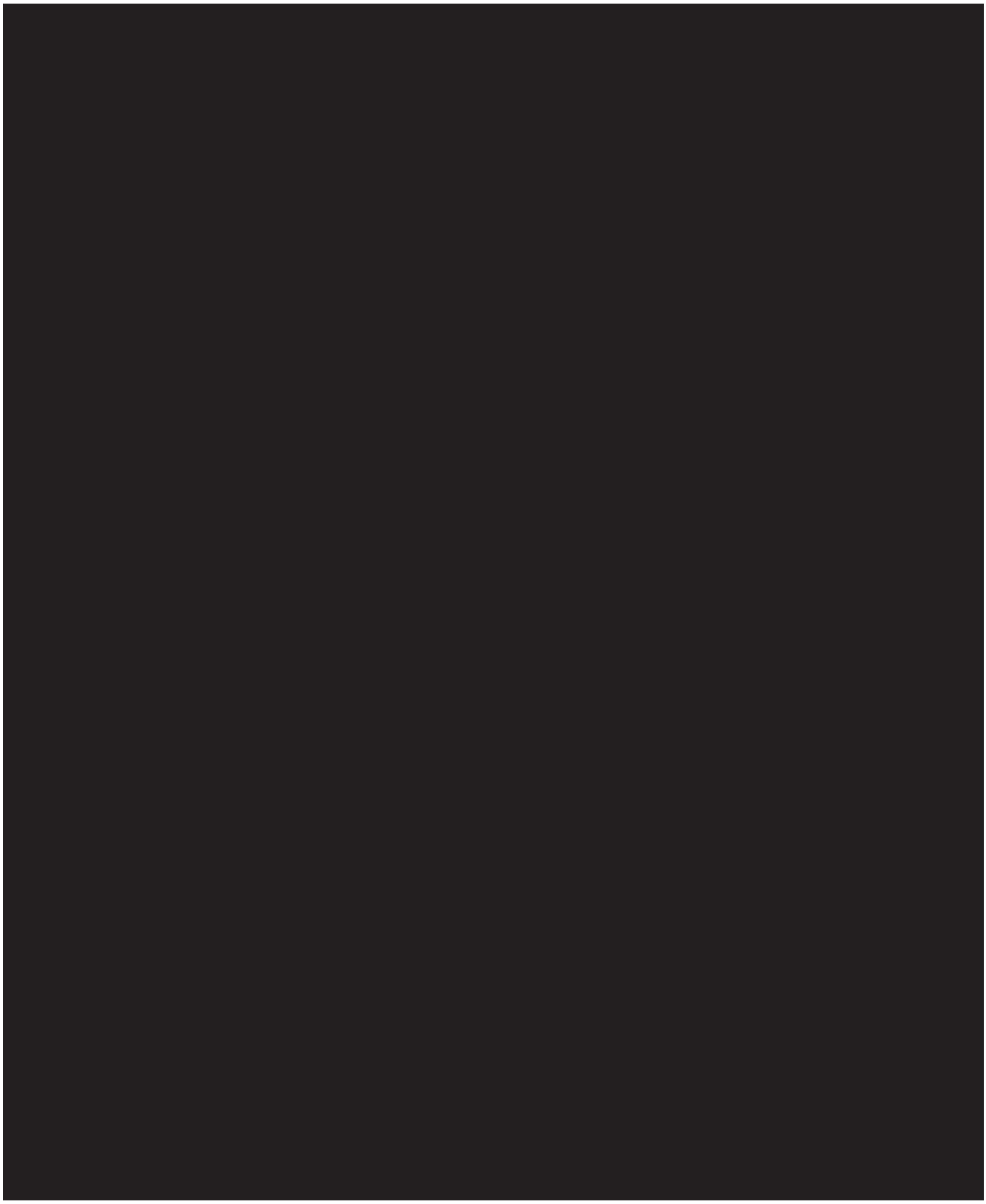




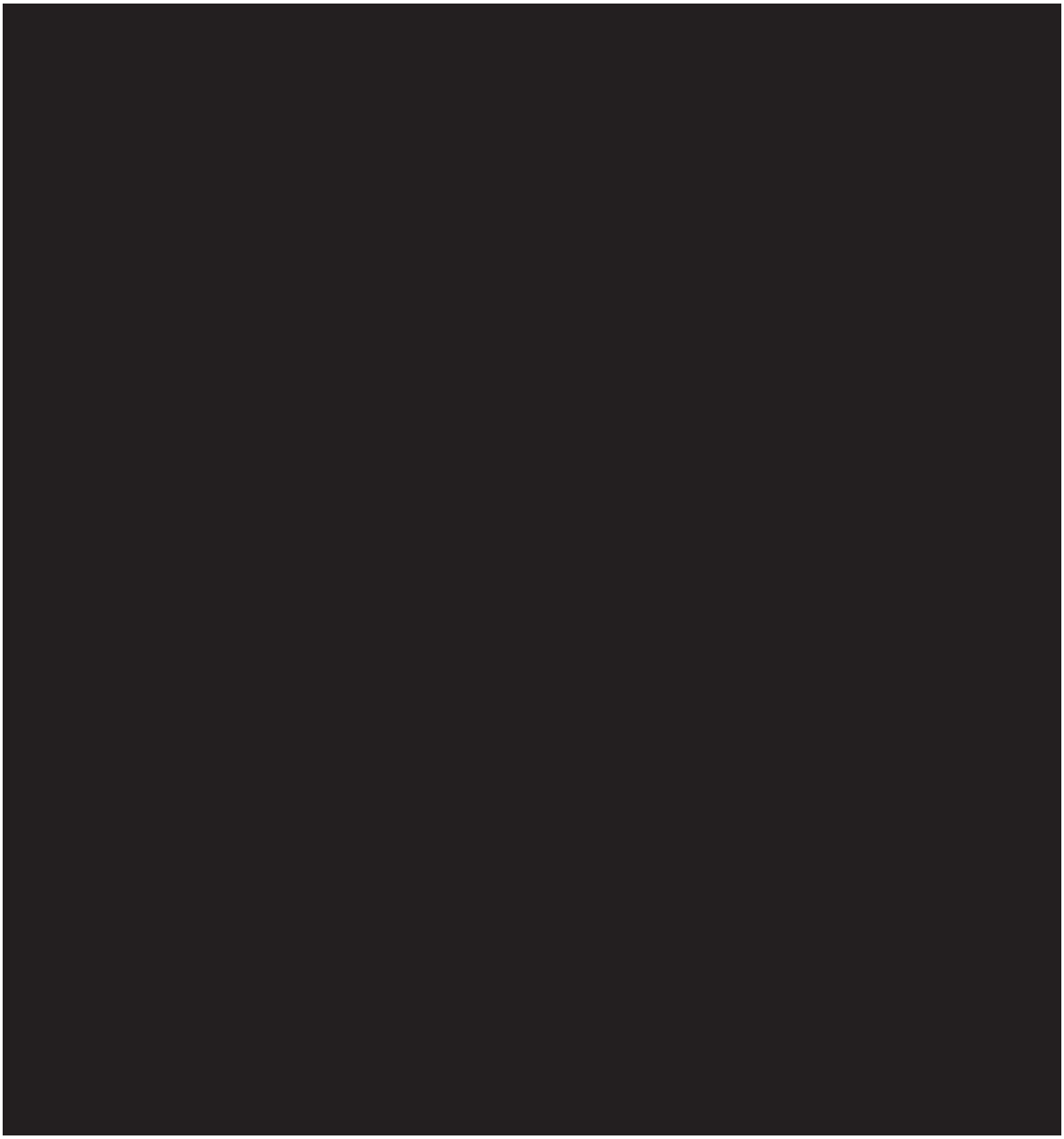


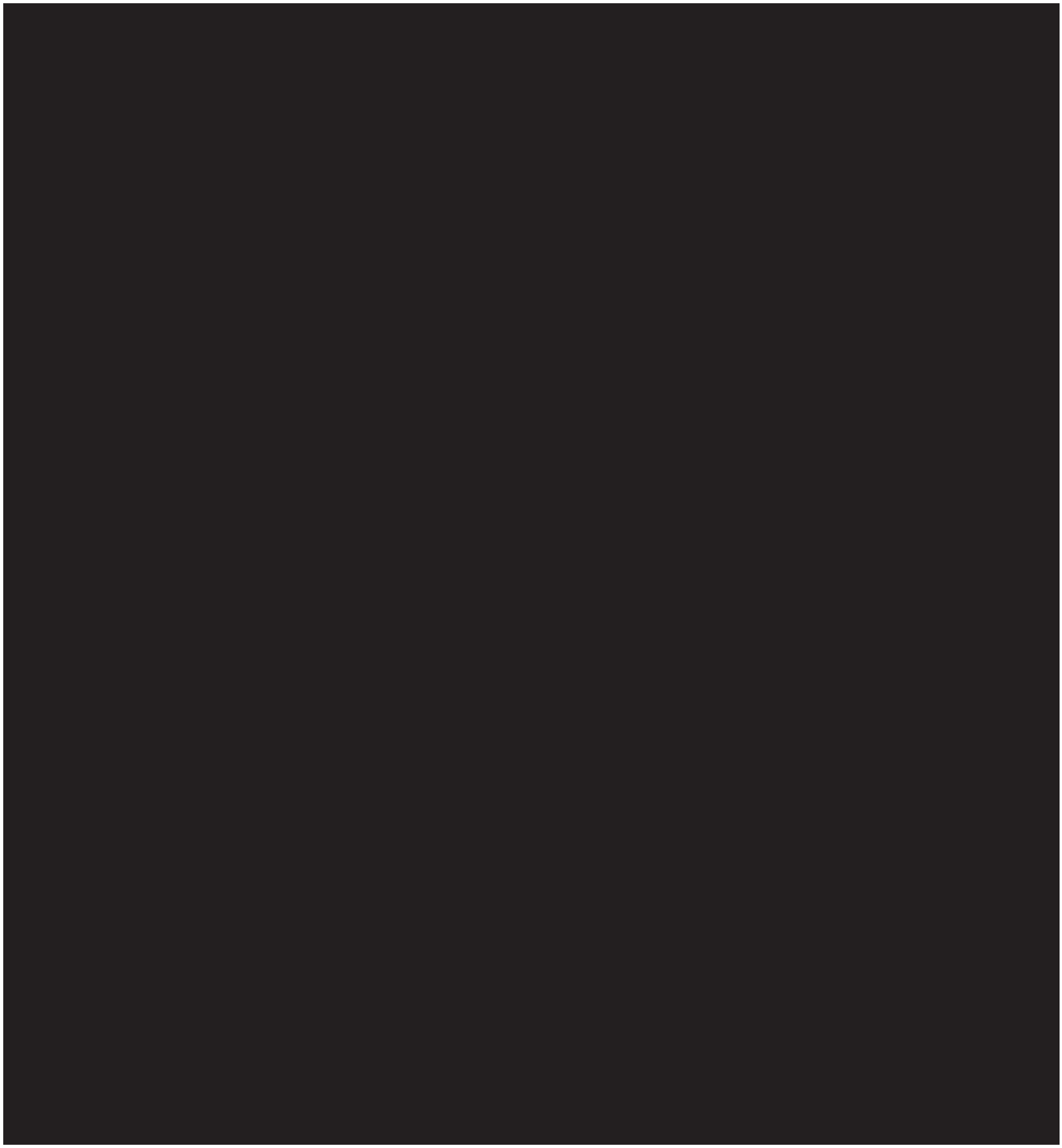






## 5.7 APPENDIX 7 FACIT-F QUESTIONNAIRE AND SCORING TRANSFORMATION





## 5.8 APPENDIX 8 POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES CRITERIA

**Potentially clinically significant abnormalities criteria**

| CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES<br>for Phase 2/3 studies (oncology excepted)<br>(From BTD-009536 - 21-MAY-2014, except for parameters eGFR and CLcr ) | | |
|---|---|---|
| **Parameter** | **PCSA** | **Comments** |
| **Clinical Chemistry** | | |
| ALT | By distribution analysis: | Enzymes activities must be expressed in ULN, not in IU/L. |
| | >3 ULN | Concept paper on DILI - FDA draft Guidance Oct 2007. |
| | >5 ULN | Internal DILI WG Oct 2008. |
| | >10 ULN | Categories are cumulative. |
| | >20 ULN | First row is mandatory. Rows following one mentioning zero can be deleted. |
| AST | By distribution analysis: | Enzymes activities must be expressed in ULN, not in IU/L. |
| | >3 ULN | Concept paper on DILI – FDA draft Guidance Oct 2007. |
| | >5 ULN | Internal DILI WG Oct 2008. |
| | >10 ULN | Categories are cumulative. |
| | >20 ULN | First row is mandatory. Rows following one mentioning zero can be deleted. |
| Alkaline Phosphatase | >1.5 ULN | Enzymes activities must be expressed in ULN, not in IU/L.<br>Concept paper on DILI – FDA draft Guidance Oct 2007.<br>Internal DILI WG Oct 2008. |
| Total Bilirubin | >1.5 ULN | Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. |
| | >2 ULN | Concept paper on DILI – FDA draft Guidance Oct 2007.<br>Internal DILI WG Oct 2008. |
| Conjugated (direct) Bilirubin | >35% Total Bilirubin (TBILI) and TBILI >1.5 ULN | Conjugated bilirubin based on a case-by-case basis. |
| ALT and Total Bilirubin | ALT >3 ULN and TBILI >2 ULN | Concept paper on DILI - FDA draft Guidance Oct 2007.<br>Internal DILI WG Oct 2008.<br>To be counted within a same treatment phase, whatever the interval between measurement. |

**CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES**

**for Phase 2/3 studies (oncology excepted)**

**(From BTD-009536 - 21-MAY-2014, except for parameters eGFR and CLcr )**

| Parameter | PCSA | Comments |
|---|---|---|
| CLcr (mL/min)<br>(calculated by 24-hour creatinine clearance) | <15 (end stage renal disease)<br>≥15 - <30 (severe decrease)<br>≥30 - <60 (moderate decrease)<br>≥60 - <90 (mild decrease)<br>≥90 (normal) | Per discussion with medical team, the 24-hour creatinine clearance collected by Labcorp will be used to derive CLcr in integer by formulas below.<br>**Conventional:**<br>CLcr (mL/min)=[Ur.24hr Aliq Creatinine (mg/dL) / Serum Creatinine (mg/dL)] * [Total Volume (mL) / Elapsed Date & Time (min)]<br>**SI:**<br>CLcr (mL/min)=[Ur.24hr Aliq Creatinine (mmol/L)] / Serum Creatinine (umol/L)] * [Total Volume (mL)/ Elapsed Date & Time (min)] *1000<br>**Note:** If elapsed time is >1680 minutes or <1200 minutes, calculation cancels as "Coll. Time criteria not met". |
| eGFR (mL/min/1.73m$^2$) | <15 (end stage renal disease)<br>≥15 - <30 (severe decrease in GFR)<br>≥30 - < 60 (moderate decrease in GFR)<br>≥60 - <90 (mild decrease in GFR)<br>≥ 90 (normal GFR) | Please refer to eGFR formulas in Section 4.3.1 |
| Creatinine | ≥150 µmol/L (Adults)<br>≥30% change from baseline<br>≥100% change from baseline | Benichou C., 1994. |
| Uric Acid<br>Hyperuricemia<br>Hypouricemia | <br>>408 µmol/L<br><120 µmol/L | Harrison- Principles of internal Medicine 17th Ed., 2008. |
| Blood Urea Nitrogen | ≥17 mmol/L | |
| Chloride | <80 mmol/L<br>>115 mmol/L | |
| Sodium | ≤129 mmol/L<br>≥160 mmol/L | |
| Potassium | <3 mmol/L<br>≥5.5 mmol/L | FDA Feb 2005. |
| Total Cholesterol | ≥7.74 mmol/L | Threshold for therapeutic intervention. |
| Triglycerides | ≥4.6 mmol/L | Threshold for therapeutic intervention. |
| Glucose | ≤ 3.9 mmol/L and < LLN | |

**CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES**

**for Phase 2/3 studies (oncology excepted)**

**(From BTD-009536 - 21-MAY-2014, except for parameters eGFR and CLcr )**

| Parameter | PCSA | Comments |
|---|---|---|
| | ≥ 11.1 mmol/L (unfasted); ≥ 7 mmol/L (fasted) | |
| Hypoglycaemia | ≤3.9 mmol/L and <LLN | ADA May 2005. |
| Hyperglycaemia | ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted) | ADA Jan 2008. |
| Albumin | ≤25 g/L | |
| CRP | >2 ULN or >10 mg/L (if ULN not provided) | FDA Sept 2005. |
| **Hematology** | | |
| WBC | <3.0 Giga/L (Non-Black); <2.0 Giga/L (Black) | Increase in WBC: not relevant. |
| | ≥16.0 Giga/L | To be interpreted only if no differential count available. |
| Lymphocytes | >4.0 Giga/L | |
| Neutrophils | <1.5 Giga/L (Non-Black);<1.0 Giga/L (Black) | International Consensus meeting on drug-induced blood cytopenias, 1991.<br>FDA criteria. |
| Monocytes | >0.7 Giga/L | |
| Basophils | >0.1 Giga/L | |
| Eosinophils | >0.5 Giga/L or >ULN (if ULN ≥0.5 Giga/L) | Harrison- Principles of internal Medicine 17th Ed., 2008. |
| Hemoglobin | ≤115 g/L (Male); ≤95 g/L (Female)<br>≥185 g/L (Male); ≥165 g/L (Female)<br>Decrease from Baseline ≥20 g/L | Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L). |
| Hematocrit | ≤0.37 v/v (Male) ; ≤0.32 v/v (Female)<br>≥0.55 v/v (Male) ; ≥0.5 v/v (Female) | |
| RBC | ≥6 Tera/L | Unless specifically required for particular drug development, the analysis is redundant with that of Hb.<br>Otherwise, consider FDA criteria. |
| Platelets | <100 Giga/L<br>≥700 Giga/L | International Consensus meeting on drug-induced blood cytopenias, 1991. |

**CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES**

**for Phase 2/3 studies (oncology excepted)**

**(From BTD-009536 - 21-MAY-2014, except for parameters eGFR and CLcr )**

| Parameter | PCSA | Comments |
|---|---|---|
| **Urinalysis** | | |
| pH | ≤4.6<br>≥8 | |
| **Vital signs** | | |
| HR | ≤50 bpm and decrease from baseline ≥20 bpm<br>≥120 bpm and increase from baseline≥20 bpm | To be applied for all positions (including missing) except STANDING. |
| SBP | ≤95 mmHg and decrease from baseline ≥20 mmHg<br>≥160 mmHg and increase from baseline ≥20 mmHg | To be applied for all positions (including missing) except STANDING. |
| DBP | ≤45 mmHg and decrease from baseline ≥10 mmHg<br>≥110 mmHg and increase from baseline ≥10 mmHg | To be applied for all positions (including missing) except STANDING. |
| Orthostatic Hypotension | | |
| Orthostatic SBP | ≤-20 mmHg | |
| Orthostatic DBP | ≤-10 mmHg | |
| Weight | ≥5% increase from baseline<br>≥5% decrease from baseline | FDA Feb 2007. |
| **ECG** | | Ref.: ICH E14 guidance (2005) and E14 Q&A (2012), and Cardiac Safety Research Consortium White Paper on PR and QRS (Nada et al. Am Heart J. 2013; 165(4) : 489-500) |
| HR | <50 bpm | Categories are cumulative |
| | <50 bpm and decrease from baseline ≥20 bpm | |
| | <40 bpm | |
| | <40 bpm and decrease from baseline ≥20 bpm | |
| | <30 bpm | |
| | <30 bpm and decrease from baseline ≥20 bpm | |
| | >90 bpm | Categories are cumulative |
| | >90 bpm and increase from baseline ≥20 bpm | |
| | >100 bpm | |

**CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES**

**for Phase 2/3 studies (oncology excepted)**

**(From BTD-009536 - 21-MAY-2014, except for parameters eGFR and CLcr )**

| Parameter | PCSA | Comments |
|---|---|---|
| | >100 bpm and increase from baseline ≥20 bpm | |
| | >120 bpm | |
| | >120 bpm and increase from baseline ≥20 bpm | |
| PR | >200 ms | Categories are cumulative |
| | >200 ms and increase from baseline ≥25% | |
| | > 220 ms | |
| | >220 ms and increase from baseline ≥25% | |
| | > 240 ms | |
| | > 240 ms and increase from baseline ≥25% | |
| QRS | >110 ms | Categories are cumulative |
| | >110 msec and increase from baseline ≥25% | |
| | >120 ms | |
| | >120 ms and increase from baseline ≥25% | |
| QT | >500 ms | |
| QTc | Absolute values (ms) | To be applied to any kind of QT correction formula.<br>Absolute values categories are cumulative |
| | >450 ms | |
| | >480 ms | QTc >480 ms and QTc>60 ms are the 2 PCSA categories to be identified in individual participants listings. |
| | >500 ms | |
| | Increase from baseline | |
| | Increase from baseline ]30-60] ms | |
| | Increase from baseline >60 ms | |

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# STATISTICAL ANALYSIS PLAN ADDENDUM

**Addendum for ACT16248 Statistical Analysis Plan (SAP) Version 2.0**

**SAR339375-ACT16248**

**A Phase 2B, randomized, double-blind, placebo-controlled, 2-stage seamless study to evaluate the efficacy, safety, pharmacodynamics, and pharmacokinetics of lademirsen (SAR339375) for once weekly subcutaneous injection in patients aged 12 years and older with Alport Syndrome**

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**STATISTICAL PROJECT LEADER:** [redacted]

**STUDY STATISTICIAN:** [redacted]

**DATE OF ISSUE: 19-Oct-2022**

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Total number of pages: 8

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# 1 BACKGROUND

The SAP Version 2.0 (dated 04 May 2022) was developed based on Amended Protocol 13 (dated 05 May 2022). Both documents were approved at Sanofi internally before the first DBL (22 Apr 2022) for the purpose of the first interim analysis for futility. This Amended Protocol 13 is a substantial amendment by amending the Phase 2 study design from Amended Protocol 11 (and Amended Protocol 12, for France only) to a Phase 2b, 2-stage seamless design with the following major modifications:

- Stage 1 consisted of study design from original Phase 2 study as described in Amended Protocols 11 and 12. The first interim futility analysis planned in Amended Protocols 11 and 12 was also kept in the Amended Protocol 13 with updates in statistical analysis method.
- Stage 2 consisted of newly enrolled participants for 96 weeks double blind treatment period.

The Amended Protocol 13 was approved at Sanofi internally. However due to study termination after first interim analysis for futility, this protocol was withdrawn from health authority (HA) submission. The latest protocol version approved globally by HA was Amended Protocol 11 and Amended Protocol 12, for France only.

# 2 PURPOSE OF ADDENDUM

The purpose of developing this study analysis plan (SAP) Version 2.0 addendum is to:

- Describe the major changes in study design for the final database lock (DBL) which are not reflected in SAP Version 2.0, and
- Explain the impact of following the internally approved Amended Protocol 13 on statistical analysis.

# 3 DESCRIPTION OF CHANGES

This SAP Version 2.0 addendum is developed prior to the final DBL (planned for 04 Nov 2022) by following decision to not start Stage 2 enrollment and study termination based on futility analysis result. As the study was terminated early, prior to all Stage 1 participants' completion of the double blind (DB) period of the study, and no Stage 2 participants are enrolled, only key endpoints are planned to be analyzed and the time frame of analysis is reduced to Week 48 for efficacy and most of the safety analyses. Only for limited key safety analyses, the analyses will include up to 96 weeks of the lademirsen treated period. No multiplicity adjustment will be performed. The modified objectives and endpoints are specified in Table 1, which is aligned with the endpoints defined in Amended Protocols 11, 12 and 13. However, there is no major change of the analysis plan regarding the statistical method. For efficacy analyses, as no Stage 2 participants are enrolled, all statistical method will only include Stage 1 participants, and the covariates only pertinent to Stage 2 participants will be removed.

**Table 1 - Objectives and endpoints for final analysis (modified after the decision of study termination)**

| Population[a] | Objectives | Endpoints |
|---|---|---|
| **Primary** | | |
| Primary population | To assess the efficacy of lademirsen in reducing the rate of decline in kidney function as compared to placebo in participants at risk for rapidly progressive Alport syndrome | Annualized rate of change in estimated glomerular filtration rate (eGFR) during the placebo-controlled treatment period |
| **Secondary** | | |
| ITT population | To assess the efficacy of lademirsen in reducing the absolute decline in kidney function at Week 48 | Absolute and percentage change in eGFR values from baseline at Week 24 and 48<br>Proportion of participants with a reduction from baseline in eGFR of <10%, <20%, <30%, or <40% at Week 24 and 48 |
| ITT population | To assess the efficacy of lademirsen in delaying time to reach the ESRD | Number and proportion of participants who reach ESRD as defined by an eGFR≤15 mL/min/1.73 $m^2$ or initiation of hemodialysis or renal transplantation (composite endpoint) during the placebo-controlled treatment period |
| Safety population for analysis during the placebo-controlled period;<br>Lademirsen population for analysis during the lademirsen treatment period | To assess the safety and tolerability of lademirsen in participants with Alport syndrome.[c] | Incidence and severity of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) during the placebo-controlled treatment period and lademirsen treatment period, respectively<br>Number of participants with PCSA in clinical laboratory parameters during the placebo-controlled treatment period<br>Number of participants with PCSA in vital signs during the placebo-controlled treatment period<br>Number of participants with PCSA in 12-lead electrocardiogram (ECG) during the placebo-controlled treatment period |

| Population[a] | Objectives | Endpoints |
|---|---|---|
| PK population | To assess plasma pharmacokinetic (PK) parameters. Concentration at 4 hours post dosing (approximate $C_{max}$ for the parent compound) for lademirsen, its active major metabolite (RG0005), and the sum of lademirsen and RG0005 (SUM) following administration of lademirsen. $C_{trough}$ will be assessed in terms of SUM only. | Plasma concentrations of lademirsen, RG0005, and SUM (lademirsen + RG0005) in Cmax samples and SUM only in $C_{trough}$ samples during the placebo-controlled treatment period |
| ADA population | To assess potential formation of anti-drug antibodies (ADAs) following administration of lademirsen. | Incidence and titer of ADAs during the placebo-controlled treatment period<br>Association of AEs with ADAs during the placebo-controlled treatment period |
| ITT population | To assess the pharmacodynamic effect of lademirsen on changes in kidney injury and function biomarkers. | Change in kidney injury and function biomarkers from baseline at Weeks 24 and 48 during the placebo-controlled treatment period:<br>• In blood: blood urea nitrogen (BUN);<br>• In urine[b]: protein/creatinine ratio, albumin/creatinine ratio, and epidermal growth factor (EGF)/creatinine ratio;<br>• In both blood and urine[b]: creatinine, Cystatin C, transforming growth factor-β (TGFβ), and neutrophil gelatinase-associated lipocalin (NGAL). |
| **Exploratory** | | |
| ITT population | To assess the effect of lademirsen on urine and blood biomarkers in Alport Syndrome participants. | Changes in exploratory biomarkers from baseline at Weeks 24 and 48 during the placebo-controlled treatment period:<br>• In both blood and urine[b]: β-2 microglobulin and connective tissue growth factor (CTGF)<br>• In urine only[b]: kidney injury molecule-1 (KIM-1)/creatinine ratio and calbindin-D28k/creatinine ratio |
| ITT population | To assess the efficacy of lademirsen in reducing the decline in hearing sensitivities at Week 48. | Change from baseline at Week 48 in degrees of hearing level recorded in both ears measured by a pure tone audiometry in the placebo controlled treatment period |

*a* The definition of population is in Table 2.

*b* Urine biomarkers will be standardized by creatinine before analysis. If the urine parameter is collected through 24-hour urine, then the standardized value will be calculated by the original value divided by 24-hour urine creatinine; else if the urine parameter is collected through instant urine, then the standardized value will be calculated by divided by instant urine creatinine.

*c* This is one of the primary objectives for Amended Protocol 11 and 12, and secondary objective for Amended Protocol 13.

**Table 2 - Populations for analyses**

| Population | Description |
|---|---|
| Randomized population | All randomized participants.<br>Participants will be analyzed according to the study intervention allocated by randomization. |
| ITT population | All randomized participants.<br>Participants will be analyzed according to the study intervention allocated by randomization. |
| Compliant ITT population | All randomized participants who received >=80% planned IMP during the double-blinded, placebo-controlled treatment period<br>Participants will be analyzed according to the intervention allocated by randomization. |
| Primary population | All randomized participants who completed the double-blinded period (the first 48 weeks) or discontinued double-blinded period early.<br>Participants will be analyzed according to the study intervention allocated by randomization. |
| Compliant primary population | All randomized participants who completed the double-blinded period (the first 48 weeks) or discontinued double-blinded period early, and received >=80% planned study intervention during the double-blinded treatment period<br>Participants will be analyzed according to the study intervention allocated by randomization. |
| Safety population | All randomized participants who received at least 1 or partial dose of study intervention. Participants will be analyzed according to the study intervention they actually received. |
| PK population | All treated participants who received at least one dose of the lademirsen in DB period and had at least one post dose PK sample collected in DB period for determination of lademirsen concentrations. |
| ADA population | All randomized participants who received at least 1 of study intervention (safety population) who had at least one post-baseline ADA sample collected in placebo-controlled, double blind period. |
| Lademirsen treated population | Randomized population who actually received at least 1 or partial dose of lademirsen during the study. |

## 3.1 NEW ANALYSIS

This new analysis was added to this addendum to align with Amended Protocols 11 and 12 because it is described in the Amended Protocols 11 and 12, however removed in Amended Protocol 13.

### 3.1.1 Proportion of participants with a reduction from baseline in eGFR of <10%, <20%, <30%, or <40% at Weeks 24 and 48

The number and proportion of participants with a reduction from baseline in eGFR of <10%, <20%, <30%, or <40% from baseline at Weeks 24 and 48, respectively, will be summarized by treatment group. In this analysis, since by the time of final analysis, all ITT participants would have had chance to complete Week 24, but some of them may not have chance to reach Week 48 yet, those participants who do not have chance to reach Week 48 will not be included in the denominator for the reduction from baseline at Week 48. Among participants included in the denominator, if any assessments performed at Week 24 or 48, respectively, regardless of scheduled or unscheduled visit, meeting the responder criteria, then the participant will be considered as a responder; otherwise this participant will be considered as a non-responder (including participants missed the assessment at this specified week). The nominal p-value between treatment groups will be calculated by Cochran-Mantel-Haenszel method (CMH) method adjusting for screening eGFR stratification factor.

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